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16. ABSTRACT

This document summarizes current knowledge about the relationships between airborne lead and consequent effects on man and his environment. The effects that have been observed to occur when airborne lead has reached or exceeded specific levels for time periods constitute the central criteria on which EPA will base a national ambient air quality standard for lead.

Although this document deals mainly with airborne lead, it also outlines other environmental routes of exposure to lead and gives approximations of the relative contributions to human exposure of the respective routes.

In man, lead primarily affects red blood cells, the central and peripheral nervous systems, soft tissues, such as liver and kidney, and bone; the latter ultimately sequesters 95% of the body's lead burden. Significant biological indices of exposure to lead include microgram quantities of lead and of erythrocyte protoporphyrin (EP) per deciliter of blood (μg/dl). Adverse effects range from elevated EP and mild anemia at 20 to 40 μg/dl--through gastrointestinal, renal, and hepatic pathologies--to severe neurobehavioral impairment at > 80 to 120 μg/dl, sometimes culminating at those levels in convulsions and abrupt death. Preschool children and developing fetuses are the populations at greatest risk.

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PREFACE

This document has been prepared pursuant to Section 108(a)(2) of the Clean Air Act, as amended, and the Administrator's action on March 31, 1976, of listing lead as a criteria pollutant. Under the Act, the issuance of air quality criteria is a vital step in a program of responsible technological, social, and political action to protect the public from the adverse effects of air pollution.

These health and welfare criteria fulfill the regulatory purpose of serving as the basis upon which the Administrator must promulgate national primary and secondary ambient air quality standards for lead under Section 109 of the Clean Air Act. The proposed standards are being published concurrently with the publication of this criteria document.

Although the preparation of a criteria document requires a comprehensive review and evaluation of the current scientific knowledge regarding the air pollutant in question, the document does not constitute a complete, in-depth scientific review. The references cited do not constitute a complete bibliography. The objective is to evaluate the scientific data base and to formulate criteria which may serve as the basis for decisions regarding the promulgation of a national ambient air quality standard for lead.

In the case of lead, as well as other air pollutants, adverse health effects are a consequence of the total body burden resulting from exposure via all routes of intake. It is necessary, therefore, to evaluate the relative contribution made by inhalation and ingestion of atmospheric lead to the total body burden.

The Agency is pleased to acknowledge the efforts and contributions of all persons and groups who have participated as authors or reviewers to this document. In the last analysis, however, the Environmental Protection Agency is responsible for its content.

DOUGLAS M. COSTLE
Administrator
U.S. Environmental Protection Agency

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ABSTRACT

This document summarizes current knowledge about the relationships of airborne lead to man and his environment. The effects that have been observed to occur when airborne lead has reached or exceeded specific levels for specific time periods constitute the central criteria on which EPA will base a national ambient air quality standard for lead.

Although this document deals mainly with airborne lead, it also outlines other environmental routes of exposure. Primary exposure to airborne lead occurs directly via inhalation, and its sources are relatively easy to identify. Secondary exposure may occur through ingestion of foods from crops contaminated by airborne lead or, especially in children, through mouthing of nonfood items and materials so contaminated. Exposures to nonairborne lead may also be direct and indirect, and routes include ingestion of foods containing lead attributable to natural uptake and to processing.

In man, lead primarily affects red blood cells, the central and peripheral nervous systems, soft tissues such as liver and kidney, and bone; the latter ultimately sequesters 95 percent of the body's lead burden. Significant biological indices of exposure to lead include microgram quantities of lead and of erythrocyte protoporphyrin (EP) per deciliter of blood (μg/dl). Adverse effects range from elevated EP and mild anemia at 20 to 40 μg Pb/dl—through gastrointestinal, renal, and hepatic pathologies—to severe neurobehavioral impairment at >80 to 120 μg Pb/dl, sometimes culminating at those levels in convulsions and abrupt death. Preschool children and developing fetuses are the populations at greatest risk.

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ABBREVIATIONS AND SYMBOLS

Å	Ångstrom (10^{-10} meter)
AAS	Atomic absorption spectroscopy
ALA	Delta-aminolevulinic acid
ALAD	Delta-aminolevulinic acid dehydratase
ALAS	Delta-aminolevulinic acid synthetase
ALA-U	Delta-aminolevulinic acid in urine
δ-ALA	Delta-aminolevulinic acid
APHA	American Public Health Association
ASTM	American Society for Testing and Materials
ASV	Anodic stripping voltammetry
b.p.	Boiling point
B.W.	Body weight
°C	Degrees Celsius (centigrade)
Ca	Calcium
Cd	Cadmium
CDC	Center for Disease Control (Atlanta, Ga.)
$(Ch_3)_4Pb$	Tetramethyl lead (also TML or Me_4Pb)
$(CH_3)_6Pb_2$	Hexamethyl lead
$(C_2H_5)_4Pb$	Tetraethyl lead (also TEL or Et_4Pb)
$(C_6H_5)_4Pb$	Tetraphenyl lead
$(C_2H_5)_6Pb_2$	Hexaethyl lead
cm	Centimeter
CNS	Central nervous system
$CO_3^=$	Carbonate ion
CP	Coproporphyrin
CPG	Coproporphyrinogen
CP-U	Coproporphyrin in urine
Cu	Copper
DA	Dopamine
dl	Deciliter
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetate
EP	Erythrocyte protoporphyrin; also erythrocyte porphyrin
EPA	U.S. Environmental Protection Agency
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
^{59}Fe	Radioisotope of iron
Fe_2O_3	Ferric oxide
FEP	Free erthythrocyte protoporphyrin; also free erythrocyte porphyrin
ft	Foot
g	Gram
GSH	Glutathione (reduced)
G-6-PDH	Glucose-6-phosphate dehydrogenase
ha	Hectare
5-HIAA	5-Hydroxyindole acetic acid
hr	Hour
IARC	International Agency for Research on Cancer
ICRP	International Radiological Protection Commission
in	Inch
i.p.	Intraperitoneal
K	Potassium
kcal	Kilocalorie
RCR	Respiratory control rate
kg	Kilogram
km	Kilometer
l	Liter
LC_1	Concentration lethal to 1 percent of recipients
LC_{50}	Concentration lethal to 50 percent of recipients
m	Meter
M	Molar
max	Maximum
Me_3PbAc	Trimethyl lead acetate
$(Me_3Pb)_2S$	Trimethyl lead sulfide
MeV	Mega electronvolts (10^6 electronvolts)
MEPPs	Miniature end-plate potentials
mg	Milligram
Mg	Magnesium
min	Minute
MMED	Mass median equivalent diameter
ml	Milliliter
mo	Month
m.p.	Melting point

MT	Metric ton
Na	Sodium
NADH	Reduced (hydrogenated) nicotinamide adenine dinucleotide
NAS	National Academy of Sciences
NASN	National Air Surveillance Networks
NE	Norepinephrine
ng	Nanogram
Ni	Nickel
nm	Nanometer
NO_3^-	Nitrate ion
NSF	National Science Foundation
NVS	Nonvolatile solids
P	Phosphorus
Pb	Lead
^{204}Pb	Isotope of Lead (^{210}Pb, etc.)
Pb^{++}	Diavalent lead ion
Pb-A	Concentration of lead in air
Pb-B	Concentration of lead in blood
$PbBr_2$	Lead bromide
PbBrCl	Lead (II) bromochloride
$PbBrCl \cdot NH_4Cl$	Lead bromochloride-ammonium chloride
$[Pb(C_2H_3O_2)_2 \cdot 2Pb(OH)_2]$	Basic lead (II) acetate
$PbCl_2$	Lead chloride
$PbCO_3$	Lead carbonate
$PbCrO_4$	Lead chromate
PbF_2	Lead fluoride
$Pb(NO_3)_2$	Lead nitrate
PbO	Lead oxide
PbO_x	Lead oxides
$(PbO)_2$	Lead oxide dimer
Pb_3O_4	Lead (IV) oxide
$Pb(OCOCH_3)_2$	Lead (II) acetate
$Pb(OH)_2$	Lead hydroxide
Pb(OH)Br	Lead (II) hydroxybromide
Pb(OH)Cl	Lead hydroxychloride
$Pb(OH)_2CO_3$	Basic lead carbonate
$PbO \cdot PbSO_4$	Basic lead sulfate
$Pb_4O(PO_4)_2$	Lead oxyphosphate

$Pb(PO_3)_2$	Lead metaphosphate
$Pb_3(PO_4)_2$	Lead orthophosphate
$Pb_5(PO_4)_3OH$	Lead hydroxqpmxqpqwzn
PbS	Lead sulfide
$PbSO_4$	Lead sulfate
PBG	Porphobilinogen
pCi	Picocurie (10^{-12} curie)
PIXE	Proton-induced X-ray emissions
pH	Log of the reciprocal of the hydrogen ion concentration
$PO_4^=$	Phosphate ion
PP	Protoporphyrin
ppb	Part per billion
ppm	Part per million
PVC	Polyvinyl chloride
RBC	Red blood cell; erythrocyte
RNA	Ribonucleic acid
s.c.	Subcutaneous
scm	Standard cubic meter
sec	Second
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SH	Sulfhydryl
SO_2	Sulfur dioxide
$SO_4^=$	Sulfate ion
^{85}Sr	Radioisotope of strontium
STEL	Short-term exposure limit
TEL	Tetraethyl lead
TML	Tetramethyl lead
TVL	Threshold value limit
USPHS	U.S. Public Health Service
Zn	Zinc
ZnS	Zinc sulfide
ZPP	Erythrocyte zinc protoporphyrin
μg	Microgram
μl	Microliter
μm	Micrometer
>	Greater than
<	Less than
~	Approximately

1. SUMMARY AND CONCLUSIONS

1.1 INTRODUCTION

The first portion of this document is devoted to lead in the environment: its physical and chemical properties; its monitoring and measurement in various environmental media; its environmental sources, emissions, and concentrations; and its transport and transformation within the environment (Chapters 3 through 7).

Chapters 8 through 13 are concerned with the effects of lead on ecosystems and, most important, on human health. Among the questions that have been specifically addressed in this document are:

1. What are the sources of lead in the environment?
2. What are the routes and mechanisms by which lead from these sources enters the body?
3. Once lead enters the body, where is it deposited?
4. Once lead is in the body, what are its health effects?
5. Are there groups within the population that are particularly vulnerable to lead?
6. What is the magnitude of the risk in terms of the number of persons exposed in various subgroups of the population?

This document has been prepared to reflect the current state of knowledge about lead — specifically, those issues that are most relevant to establishing the objective scientific data base that will be used to recommend an air quality standard for lead that will adequately safeguard the public health.

1.1.1 Potential Exposure to Environmental Lead

Lead is unique among the toxic heavy metals in that it is relatively abundant in the earth's crust. Because of its easy isolation and low melting point, lead was among the first metals to be used by man thousands of years ago. The environmental significance of lead is a result both of its utility and of its abundance. World production exceeds 3.5 million tons/year, a far larger quantity than the production of any other toxic heavy metal.

Lead is present in food, water, air, soil, dustfall, paint, and other materials with which the general population comes in contact. Each of these represents a potential pathway for human lead exposure via inhalation or ingestion. The actual lead content in each source may vary by several orders of magnitude. Potential exposure patterns are further confounded by human activity patterns and by differences between indoor and outdoor environments. The number and extent of variables involved make it very difficult to determine the actual lead intake of individuals in their normal environment.

As a result of centuries of the mining, smelting, and use of lead in human activities, natural background concentrations are difficult to determine. Geochemical data indicate that the concentrations of lead in most surface materials in the United States range from 10 to 30 ppm (μg/g). Trace amounts of lead occur naturally in air and water as a result of wind and rain erosion, and in air as a result of volcanic dusts, forest fires, sea salt, and the decay of radon. Natural background concentrations of airborne lead have been estimated to approximate 0.0006 μg Pb/m^3 of air (or 5 x 10^{-7} μg Pb/g air). Natural concentrations in fresh water have been estimated to be about 0.5 μg/liter of water (about 5 x 10^{-4} μg Pb/g water) and in ocean water about 0.05 μg Pb/liter of water (about 4.9 x 10^{-5} μg Pb/g water). As a consequence of the extensive and diverse uses of lead, present concentrations of lead in air, soil, and water are substantially higher than these estimated background levels. Nonurban lead concentrations average 0.1 μg Pb/m^3 of air (about 8 x 10^{-5} μg Pb/g air). Concentrations of airborne lead in U.S. cities, at sites not conspicuously influenced by major sources, average 1 μg Pb/m^3 of air (8 x 10^{-4} μg Pb/g air). Expressed on a weight basis with respect to the total suspended particulate (TSP) in the air, this amount is approximately equivalent to 10^4 μg Pb/g TSP.

The shape of buildings in urban areas may cause large horizontal and vertical variations in lead concentrations. In the absence of such structures, the vertical gradient would usually be relatively small. During periods of maximum traffic density on freeways, airborne concentrations of lead immediately adjacent to the freeways may reach 20 $\mu g/m^3$ for a few hours. In the immediate vicinity of large stationary sources having no air pollution controls, concentrations of airborne lead may reach 300 $\mu g/m^3$ under unfavorable meteorological conditions. Consequently, exposure via inhalation of airborne inorganic lead particulates may vary by a factor of at least 100, depending on location and activity patterns. The small number of indoor air lead studies conducted have shown indoor concentrations to be one-third or less the level measured outdoors. Indoor levels vary widely depending on type of structure, air conditioning, wind, etc.

Dust is a generic term and consequently imprecise when used to describe potential human exposure. Dust in the popular sense usually refers to solid particles that have settled on a surface and that can be readily redispersed in the atmosphere. In an aerometric sense, dust is solid particles suspended in the atmosphere; consequently, it is an integral part of total suspended particulates. In an occupational sense, dust may encompass even larger particles discharged into the work environment by mechanical means. Dustfall is a measure of the settled particulate, or that deposited in or on the collection devices; thus dustfall is more closely related to the popular definition of dust. In this document, dustfall is treated as a separate pathway for potential exposure to lead via ingestion of these settled particles, but only in a qualitative manner.

Lead concentrations in dustfall vary widely with the type and distribution of sources. The highest values occur in the immediate vicinity of sources and diminish rapidly with distance. Potential exposure to lead in dustfall depends on the total accumulation of dust in accessible areas. The accumulation depends on the deposition rate and the frequency and efficiency with which accessible surfaces are cleaned. Lead accumulation resulting from deposition from the air may be augmented in the homes of lead workers by transportation of lead-containing dusts from the workplace. The level of accumulated lead potentially available both indoors and outdoors clearly may vary by one to two orders of magnitude.

Concentrations of lead in solution in most urban water supplies are below 10 μg Pb/liter of water (0.01 μg Pb/g water), but some values >50 μg/liter (the U.S. Public Health Service standard for lead in drinking water) have been reported. Suspended solids contain the major fraction of lead in river waters. Concentrations of lead in tap water may be considerably higher than those in municipal supplies. Lead values as high as about 2000 μg/liter have been reported for homes with lead pipes and lead-lined storage tanks.

Sea spray, rainwater leaching, and flaking paint from older buildings can contribute significantly to lead levels in adjacent soil. Direct ingestion of the soil or of re-entrained dust, as well as ingestion of the paint chips themselves, constitute an important source of lead in areas where these conditions exist.

The contribution of food to human exposure to lead is highly variable and not well quantified. Estimates of daily intake vary from about 100 to 350 μg Pb/day. Recent studies in the Unitd States estimate the adults ingest about 200 μg Pb/day in food. Beverages and foods that are stored in lead-soldered cans or stored or served in lead-glazed pottery have been identified as having high lead content. Processed milk has been reported to contain more lead than fresh cow's milk — about 20 to 40 μg/liter compared to about 5 to 10 μg/liter, respectively. If these values are correct, processed milk could be a significant source of lead exposure for infants.

For adults, illicitly distilled whiskey and old automobile batteries used as home heating fuel represent two nonindustrial sources of overt lead poisoning. Of much greater significance as a health problem, however, are various sources of occupational exposure.

Workers involved in uncontrolled (without pollution controls) mining, smelting, and manufacturing processes where lead is used, have the highest level of potential exposure. Although occupational conditions have generally been substantially improved, in some cases lead concentrations in the air in work places have been measured at 1000 $\mu g/m^3$ or greater. The major occupational exposure problems occur where adequate hygiene programs have not been implemented or where individuals fail to take the recommended precautions. The major route of occupational exposure is the inhalation of dust and fumes; in addition, dust transported on clothing from the work place to the home or automobile may be a significant pathway of exposure for workers and their families.

1.1.2 **Sources of Environmental Lead**

The mining, smelting, and use of lead in human activities has significantly altered the natural distribution of lead in the environment. Contamination has occurred primarily in the vicinity of sources and in densely populated areas.

The lead used in gasoline antiknock additives represents a major fraction of the total U.S. lead consumption, and motor vehicle emissions constitute the major source of lead emissions to the atmosphere. In 1975, some 189,000 MT of lead (16 percent of total production) used in antiknock compounds were converted to 142,000 MT of atmospheric emissions (88 percent of total lead emissions). As a result of legislation setting a maximum limit on the lead content of gasoline, the production and use of alkyl lead additives has decreased in recent years and will probably continue to do so.

Based on 1975 estimates, combustion of waste oil and incineration of solid waste are the major contributors of lead emissions from stationary sources (12,060 MT/year). This figure represents only that portion of waste oil that is reprocessed and burned in oil-fired or coal-fired boilers and municipal incinerators. Other stationary sources of lead emissions include iron and steel production in plants with poor pollution controls, primary and secondary smelting, battery manufacturing, and lead alkyl manufacturing. Lead that may be emitted to the environment from these operations includes that in stack emissions and fugitive dusts. Contamination from the major stationary emitters may determine environmental concentrations for a radius of several kilometers around the sources. Fugitive dusts may result in a high level of contamination in the immediate vicinity of small, uncontrolled battery recycling operations.

In terms of mass balance, lead from mobile and industrial sources is transported and distributed mainly via the atmosphere. Certain waste disposal operations that discharge large amounts of lead into soil and water result only in highly localized contamination. Lead is emitted to the atmosphere primarily in the form of inorganic particulates; however, small amounts of organic vapors have been reported in the vicinity of gasoline service stations, garages, and heavy traffic areas. These organic vapors undergo photochemical decomposition in the atmosphere, but they may also be adsorbed on dust particle surfaces.

Based on the limited data available, it is estimated that 75 percent of the particulate lead emitted from automobiles is removed from the atmosphere in the immediate vicinity of traffic sources.

Particles smaller than those from mobile sources, and emissions from tall stacks will remain airborne longer and be transported over greater distances. Submicron particles may reside in the atmosphere a week or more before they are removed by dry deposition (diffusion and inertial mechanisms) and by precipitation. The tendency toward uniform vertical and horizontal distribution (mixing with concomitant distribution) increases with an increase in residence time.

The chemistry of lead aerosols discharged into the environment has not been studied as extensively as the chemistry of some of the other major air pollutants. Much of the work on lead particulate chemistry before 1973 was limited to elemental analyses and did not include analyses of associated ions. Information from elemental analyses is not sufficient to permit a thorough examination and understanding of (1) transformation and transport processes that occur among the environmental media, (2) mobility of lead in soils, (3) uptake and distribution of lead in plants, and (4) the overall impact of lead pollution on human health and ecosystems. Information is needed on the chemical forms and interactions of lead and its tendency to form compounds of low solubility with the major anions. Only a few studies have been conducted on the chemical forms of lead in soil and plants. They show that the principal lead form found in soils is sulfate, and the principal form found in plants is phosphate.

Lead dissolved from primary lead sulfide ore tends to combine with carbonate or sulfate ions to form relatively insoluble lead carbonate or lead sulfate, or to be absorbed by ferric hydroxide. The amount of lead that can remain in solution in water is a function of the concentration of other ions, especially hydrogen ions.

1.1.3 **Monitoring of Environmental Lead**

Lead has been monitored in air, water, soil, food, and biological samples such as blood and urine for many years, but the accuracy of the early sampling and analytical techniques was quite low. Consequently, these earlier data can be used only in a qualitative or semiquantitative manner. External contamination has been the major problem in all sampling procedures, particularly in sampling for blood lead analyses. Sampling and analytical techniques for environmental lead have enjoyed considerable improvement and refinement in the past few years. Some of the best methods, however, are tedious and expensive and are available only in relatively specialized laboratories. Those analytical techniques that are less sophisticated produce results of limited value. The capability now exists for achieving high precision in lead monitoring; but in general practice, precise and accurate results are difficult to obtain, particularly for biological samples. Atomic absorption spectroscopy is the most successful analytical method used in recent years. The primary problem faced in environmental monitoring — that is, sampling and analysis — is to determine the type of monitoring procedures to be used to accomplish specific objectives, and to establish and maintain adequate quality control.

Ambient air monitoring procedures designed specifically for assessing population exposure patterns present particularly difficult problems. Total mass concentration, particle size distribution, and chemical composition of lead aerosols all vary considerably with space and time. In using atmospheric measurements to determine population exposures, human activity patterns are a further complication. Thus the relationship between measurements of atmospheric concentration of lead, duration of exposure, and incremental changes in blood lead levels is not constant. Although measurements of atmospheric lead levels are an essential ingredient in population exposure assessment, other indices of exposure such as blood lead and free erythrocyte porphyrin (FEP) levels are also essential for the characterization of human population exposures.

Blood lead may be measured by several general techniques that presently appear to be satisfactory in the hands of qualified analysts who have a sophisticated technical appreciation of the many problems associated with measuring an element that is both present at trace levels and ubiquitously distributed as a contaminant. Extensive interlaboratory comparisons have demonstrated the need for standardizing methodology, using reference standards, and obtaining blood lead determinations from those laboratories having highly skilled personnel accustomed to handling a large number of samples. The present existence of a number of regional and national analytical proficiency testing programs will help improve the quality of analysis and the reliability of consequent clinical and epidemiological data. Measurements of biological indicators such as erythrocyte porphyrin, δ-ALA, and δ-ALAD are also a problem. A standardized method exists for urinary ALA, and a program is underway in the United States to evaluate standardizations of methodology for determining erythrocyte porphyrin.

1.2 EFFECTS OF LEAD ON MAN AND HIS ENVIRONMENT

In the summary material presented in the preceding section, attention was directed to all the exposure aspects of lead. The biological aspects of the lead pollution problem are discussed in this section. These aspects include not only the effects of lead on man, but also its effects on a myriad of ecosystems that support man and contribute to his general welfare.

1.2.1 Effects of Lead on Man

The effects of lead on man are summarized in sequential statements of present knowledge concerning:

1. Man's metabolism of lead.
2. Biological and adverse health effects in man.
3. Effects of lead on populations.
4. Risks man incurs from exposure to lead.

1.2.1.1 METABOLISM

Metabolism, as discussed here, encompasses the physiological processes in man that relate to absorption, distribution, excretion, and net retention. It can be discussed in terms of routes of lead exposure and the physiological distinctions existing within certain segments of the population that modify these processes. Special attention is focused on the factors that may place the developing fetus and the child in a category of higher risk than the adult.

Nearly all lead exposures result from inhalation and ingestion. The quantities of lead absorbed via these routes are determined by many factors such as the physical and chemical form of the lead, and the nutritional status, metabolic activity, and previous exposure history of those exposed.

Clinical studies on the desposition of airborne lead particulate matter in the human respiratory tract suggest that 30 ± 10 percent of the ambient air lead particulates inhaled will be deposited. Of the lead thus deposited in the respiratory tract, it has been estimated that as much as 50 percent or more is absorbed and enters the blood stream. This deposition may vary considerably, depending on particle size and pattern of respiration. Part of the fraction deposited in the respiratory tract, that portion removed via the mucociliary escalator, is swallowed and enters the gastrointestinal tract. Animal studies suggest that the relative efficiency of lung clearance mechanisms may be impaired at high levels of airborne lead.

In children, approximately 40 percent of the lead taken into the gastrointestinal tract is absorbed, whereas the corresponding value for adults is about 10 percent. In one study assessing net gastrointestinal absorption, an inverse relationship between calcium intake and lead absorption was shown. This relationship has also been demonstrated in experimental animals.

In discussing the routes by which man may be exposed to environmental lead, it is important to distinguish between primary and secondary exposure to atmospheric lead. Primary exposure is direct, and secondary is indirect. Primary exposure to airborne lead consists of its direct inhalation, whereas secondary exposure to airborne lead consists of ingestion of lead that is of atmospheric origin (that is, lead that is transported by the airborne route to the ingested material).

Lead may contaminate foodstuffs by atmospheric fallout, with subsequent adsorption onto plant surfaces or absorption into plants. This contamination may involve primary food (plants consumed by man) or animal food crops. Soil lead taken into plants may come from atmospheric fallout or from leaching from natural as well as industrial sources. The absorption of soil lead by plants, however, is thought to be relatively poor, although data on lead accumulation in tree rings suggest that absorption from soil may occur in at least some plants. In any case, the contribution of air lead to food lead levels is probably small on the basis of a nationwide food distribution system; but adequate quantification does not yet exist to allow precise statements on this point to be made. It is clear, however, that commercial processing raises the lead content of food significantly.

Another important depot of lead in the environment is soil or dust. The ultimate source of this lead varies from place to place; it can be dustfall from the atmosphere (coming from either stationary or mobile sources), or it can be soil or dust into which leaded paint has eroded. This exposure route is thought to be more important for children than for adults. Studies have consistently shown associations between soil or dust lead levels and blood lead levels in children when such exposures exceed 1000 ppm. It is thought that lead reaches the children through their normal mouthing behavior. Lead is picked up on children's hands through their play and is then transferred to their mouths by their customary habit of putting their hands, objects, and materials in their mouths. There is evidence demonstrating a relationship between dust lead and lead on fingers, but as yet there is no direct evidence linking lead on fingers with lead in the blood. In children with pica, however, the importance of this source could be greatly magnified.

It has been shown repeatedly that levels of lead in blood increase when oral intake increases, but studies do not show a precise, quantitative expression of this relationship. Rather, a number of studies show that, with sustained daily ingestion of 100 μg of lead, the maximum increase in steady-state levels of blood lead ranges from 6 to 18 μg/dl. These variations probably relate to nutritional factors, biological variability, unreported sources of exposure, differences in analytical techniques, or previous exposure history — or to a combination of these factors. Since children, particularly infants, absorb a larger percentage of lead than adults do, the relative contribution of oral intake is undoubtedly greater for them. Because of higher metabolic activity, children also inhale relatively more airborne lead than do adults. Therefore, the contribution of airborne lead to total lead intake may be greater in children than in adults, but one must keep in mind that children also eat correspondingly more on a body weight basis.

A number of experimental animal studies have assessed the effects of nutrition and other factors on gastrointestinal absorption as reflected by blood lead levels. It is clear from these studies that the status of essential nutrients such as calcium, iron, phosphorus, fat, and protein is very important.

The absorption, distribution, and accumulation of lead in man is conveniently described by a three-compartment model. The first compartment, circulating red blood cells, distributes lead to the other two, soft tissues (primarily liver and kidney) and bone, where it accumulates. This accumulation begins in fetal life as a result of transplacental transfer. In nonoccupationally exposed adults, such storage approaches 95 percent of the total body burden. The skeleton is a repository of lead that reflects the long-term cumulative exposure of the individual; body fluids and soft tissues reflect more recent exposure.

Since the nonaccumulating body burden in soft tissues has a greater toxicological significance than that fraction sequestered in bone, the mobilizable lead burden is a more important concept than total body burden. In this connection, chelatable urinary lead has been shown to provide an index of the mobile portion of the total body burden, as has the lead level in blood, which is the more generally used indicator of internal dose.

There is a time frame in which changes in exposure register as a perturbation in the blood lead level. Clinical studies show that (1) a controlled daily intake results in a constant concentration of blood lead after 110 days, depending on the exposure setting, and (2) a single, acute, controlled exposure yielded a blood lead half-life of about 2 days compared to approximately 17 days in the case of repeated exposures. Following cessation of exposure after long exposure periods (e.g., years), however, the half-life of blood lead can be expected to be substantially longer than 17 days.

Fecal excretion represents the major route by which ingested lead is eliminated from the body. Though excretion by this route is usually much greater than by urinary elimination, the total fecal lead content includes unabsorbed lead as its major component.

1.2.1.2 BIOLOGICAL AND ADVERSE HEALTH EFFECTS OF LEAD IN MAN

There are various physiological levels and exposure ranges at which the effects of lead in man occur. Furthermore, lead affects man at the subcellular, cellular, and organ system levels.

Among subcellular components, both nuclei and mitrochondria generally show the most pronounced responses to cellular invasion by lead. The mitochondria, however, are most vulnerable and sustain the greatest functional impairment. Mitochondrial injury, both in terms of cellular energetics and morphological aberration, has been shown in a number of experimental animals. In man, the evidence for mitochondrial impairment has been morphological rather than functional. Those subcellular changes observed are primarily the development of nuclear inclusion bodies in kidney cells as well as mitochondrial changes in renal tubular cells in persons exposed occupationally.

Any discussion of the subcellular effects of lead must consider the question of chromosomal aberrations and carcinogenesis. At the present time, no conclusive statements can be made about the induction of chromosomal damage by lead. The literature on this issue either yields conflicting information or describes studies that are difficult to compare with each other. Some experimental animal studies relate the development of cancer to relatively high doses of lead, but as is true in the case of other suspected carcinogens, there are no data corroborating these findings in man.

Among the systemic and organic effects of lead, important areas are its hematologic, neurobehavioral, and renal effects. Attention must also be given, however, to the effects of lead on reproduction and development as well as its hepatic, endocrine, cardiovascular, immunologic, and gastrointestinal effects.

A number of significant effects of lead on the hematopoietic system in humans have been observed in lead poisoning. These effects are prominent in clinical lead poisoning but are still present to a lesser degree in persons with a lower level of lead exposure.

Anemia is a clinical feature of lead intoxication, resulting from both increased erythrocyte destruction and decreased hemoglobin synthesis. In children, a threshold blood lead level for production of these symptoms of anemia is approximately 40 μg Pb/dl, and the corresponding value for adults appears to be 50 μg Pb/dl.

Hemoglobin synthesis is impaired by lead via inhibition of synthesis of the globin moiety and inhibition at several steps in the synthesis of heme. The step most sensitive to lead in the heme synthetic pathway is that mediated by the enzyme δ-aminolevulinic acid dehydratase (δ-ALAD), which connects two units of δ-aminolevulinic acid (δ-ALA) to form porphobilinogen. The result is an increase in plasma level and enhanced urinary excretion of δ-ALA. Also inhibited by lead is the incorporation of iron into protoporphyrin to form heme, the prosthetic group of hemoglobin. This results in the accumulation of coproporphyrin, which is excreted in the urine, and of protoporphyrin, which is retained in the erythrocytes. The overall effect of lead is a net decrease in heme synthesis. (This also derepresses δ-ALA synthetase, the enzyme involved in the first step of heme synthesis.)

Inhibition of δ-ALAD occurs at extremely low blood lead levels and has been shown to start at a blood lead level as low as 10 μg/dl. Though the health-effect significance of inhibition at a blood level of 10 μg/dl is open to debate, the increased urinary δ-ALA excretion that occurs with increasing inhibition at 40 μg/dl is accepted as a measure of probable physiological impairment *in vivo*. This threshold level for urinary δ-ALA excretion (40 μg/dl) appears to be true for both adults and children.

An increase in free erythrocyte protoporphyrin (FEP) occurs at blood lead levels of 16 μg/dl in children. In adult females, this threshold is probably similar. In adult males, the value is 20 to 25 μg/dl. The precise threshold for coproporphyrin, while not well established, is probably similar to that for δ-ALA. Elevation of free erythrocyte protoporphyrin has the same implications of physiological impairment *in vivo* as urinary δ-ALA. To the extent that the protoprophyrin elevation is a likely indicator of the impairment of mitochondrial function in erythroid tissue, it may be even more important. For these reasons, physicians who participated in the development of the 1975 statement by the Center for Disease Control and the American Academy of Pediatrics reached a consensus that elevated FEP should be used as an indicator of increased exposure to lead.

The effects of lead on the nervous system range from acute intoxication and fatal encephalopathy to subtle behavioral and electrophysiologic changes associated with lower level exposures. Changes throughout the range of effects are related to blood lead levels.

It would appear that surprisingly low levels of blood lead may sometimes be associated with the most extreme effects of lead poisoning — servere, irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathy symptoms and/or death. Though for most adults such damage does not occur until blood lead levels substantially exceed 120 μg/dl, some evidence suggests that acute encephalopathy and death may occur in some adults at blood lead levels slightly below 100 μg/dl. For children, the effective blood levels for producing encephalopathy or death are lower than for adults, with such effects being seen somewhat more often, starting at approximately 100 μg/dl. Again, however, evidence exists for the occurrence of encephalopathy in a very few cases at lower levels, down to about 80 μg/dl.

It should be noted that once encephalopathy occurs, death can be a frequent outcome, regardless of the level of medical intervention at the time of the acute crisis. It is also crucial to cite the rapidity with which acute encephalopathy or death can develop in apparently asymptomatic individuals or in those apparently only mildly affected by elevated body burdens of lead. It is not unusual for rapid deterioration to occur, with convulsions or coma suddenly appearing and progressing to death within 48 hr.

This suggests that at high blood lead levels, even when individuals are asymptomatic, rather severe neural damage can exist without overt manifestations. Studies show that apparently asymptomatic children with high blood lead levels of over 80 to 100 μg/dl are permanently impaired cognitively, as are individuals who survive acute episodes of lead encephalopathy. These studies tend to support the hypothesis that significant if albeit subtle changes in neural function occur at what were once considered tolerable blood lead levels.

Other evidence tends to confirm rather well that some type of neural damage does exist in asymptomatic children, and not necessarily only at very high levels of blood lead. The body of studies on low- or moderate-level lead effects on neurobehavioral functions present overall an impressive array of data pointing to that conclusion. Several well-controlled studies find effects that are clearly statistically significant, and many others report nonsignificant but borderline effects. Since some of the effects at low levels of lead exposure discussed in this document are of a subtle nature, the findings are not always striking in individual cases. Nevertheless, when the results of all of the studies on neurologic and behavioral effects at subclinical exposures are considered in an overall perspective, a rather consistent pattern of impaired neural and cognitive functions appears to be associated with blood lead levels below those producing the overt symptomatology of lead encephalopathy. The blood lead levels at which neurobehavioral deficits occur in otherwise asymptomatic children appear to start at a range of 50 to 60 μg/dl, although some evidence tentatively suggests that such effects may occur at slightly lower levels for some children.

Data obtained for the effects of lead on the nervous system in laboratory animals are also quite extensive. Encephalopathy is produced by high-level perinatal exposure to lead; in different species, this occurs to varying degrees as characterized by the relative extent of neuronal degeneration and vasculopathy. It seems clear that the animal data support the contention that the developing organism represents the population at greatest risk for central nervous system toxicity.

There is also good evidence that perinatal exposure of laboratory animals to lead at moderate levels will produce delays in both neurological and sexual development. Since these effects have been demonstrated to occur in the absence of either undernutrition or growth retardation, it has been suggested that they may represent more or less direct effects of lead in the respective systems.

In animal studies, locomotor activity has been the most commonly used behavioral index of lead toxicity. Data indicate that increased locomotor activity in young animals occurs only at moderately high exposure levels. It may be, in view of the levels, that the changes in activity currently reported in laboratory animals are more diagnostic of a post-encephalopathic hyperactivity than of subclinical effects. Interestingly, the reactivity changes seen in older animals are associated with much lower blood lead levels.

Finally, reports on the effects of lead exposures on the acquisition and/or performance of operant responses indicate that perinatal exposure to moderate or low levels of lead may disrupt this type of behavior. Thus at blood lead levels ranging from 30 to 80 µg/dl, cognitive function appears to be disrupted in animals.

Excessive lead exposure can result in acute as well as chronic renal injury in man. The acute renal effects of lead are seen in persons dying of acute lead poisoning where lead-induced anemia and/or encephalopathy may also be seen. These effects are manifested by nonspecific degenerative changes in renal tubular lining cells, cloudy swelling, and some degree of cellular necrosis. In addition, nuclear inclusion bodies form in tubule cells, and there are functional and ultrastructural changes in tubular mitochondria. Aminoaciduria, glycosuria, and hyperphosphaturia are noted, with aminoaciduria being a rather consistent feature of tubular damage in children. These effects are usually reversible. It is not possible at the present time to state what level of lead in blood is associated with aminoaciduria or any of the other specific indices of acute renal injury.

Prolonged lead exposure in humans can result in chronic lead nephropathy. The pathology of these chronic changes is different from that seen in acute renal injury. It is characterized by the gradual onset of pronounced arteriosclerotic changes, fibrosis, glomerular atrophy, hyaline degeneration, and reduction in kidney size. This can be a progressive, irreversible condition resulting in death from renal failure. A threshold of lead exposure for these chronic changes cannot yet be stated, however, as a result of the typical inaccessibility of data needed for the accurate assessment of the preceding long-term exposure history.

Considerable evidence for the adverse effects of lead on reproduction and development in man has been accumulating for many years. Many of the early data on the induction of abortions, stillbirths, and neonatal deaths were for occupationally exposed pregnant women, where such effects were demonstrated at high blood lead levels. Of more pressing present interest are certain recent studies in this area focusing on two aspects of the effects of low to moderate lead exposure on reproduction: gametotoxicity and post-conception events.

In regard to potential lead effects on human ovarian function, one study has shown that short-term exposure at ambient air levels of less than 7 $\mu g/m^3$ may cause an increase in the anovular cycle and disturbances in the lutein phase. This study, however, requires confirmation before conclusive statements can be made. Another recent report involving occupational exposure similarly suggests that moderately increased lead absorption (blood lead mean = 52.8 µg/dl) may result in direct testicular impairment; however, the design of this study is such that this observation also requires verification.

Thus, it is clear that gametotoxic, embryotoxic, and teratogenic effects at a gross level can be induced in laboratory animals with lead, but it should be emphasized that the production of such effects probably requires acute, high exposures. Unfortunately, a paucity of information exists on the teratogenicity and developmental toxicity of chronic low or moderate lead exposures. Available data on the subject do suggest, however, that chronic low-level lead exposure may induce postnatal developmental delays in rats.

Our present knowledge about the effects of lead in man on the hepatic, cardiovascular, immunologic, and endocrine systems is fragmentary, rendering it difficult to make any conclusive statements about quantitative relationships. For example, effects of lead on the endocrine system are not well defined at present. Thyroid function in man, however, has been shown to be decreased in occupational plumbism. Also, effects of lead on pituitary and adrenal function in man have been observed, with decreased secretion of pituitary gonadotrophic hormones being noted but adrenal function effects being a less consistent finding.

The response of the hepatic system to lead has not been well characterized in man; instead, much of the literature deals with hepatic effects in experimental animals. Lead-poisoned animals show significantly impaired drug-metabolizing activities, thus suggesting an effect on the hepatic mixed-function oxidase system. Since detoxification in animals depends on the microsomal heme protein, cytochrome P450, and since heme biosynthesis is impaired in lead exposure, such an effect is a logical consequence of lead poisoning.

Of more direct interest in terms of reproductive efficiency are the effects of lead exposure on pregnant women — not only on fetal health and development, but also on maternal complications. Placental transfer of lead has been demonstrated both by fetal tissue analysis and comparison of newborn umbilical cord blood lead with maternal blood lead. One must not only consider the resulting absorption of lead by the fetus, but also the specific points in embryonic development at which exposure occurs. Fetal tissue uptake of lead occurs by the end of the first trimester, which may be a sensitive period in embryonic development of the nervous system.

Studies comparing umbilical cord blood lead levels in newborns with simultaneously sampled maternal blood show that the newborn and maternal levels are closely correlated. The studies have also shown that the newborns of mothers in an urban setting are born with generally higher blood levels than those of corresponding newborns from rural areas.

That the prenatal exposure of the fetus to lead, even in the absence of teratogenic effects, is of consequence for adverse health effects is shown by studies relating fetal levels to changes in fetal heme synthesis and to the incidence of premature births. Some suggestions in the literature that heme biosynthesis in a newborn may be affected require confirmation.

In evaluating maternal complications related to lead exposure, one must consider that pregnancy is a physiological stress that may place the pregnant woman at higher risk to lead exposure effects. Both iron and calcium deficiency increase the susceptibility of an individual to lead toxicity. Women have an increased risk of both deficiencies during pregnancy and postpartum.

Some available but unconfirmed information indicates that the risk of premature rupture of the amniotic membrane may be higher in cases of elevated exposure than in age-matched controls without such exposure.

The literature leaves little doubt about the deleterious health effects of lead on reproduction, but most reports do not provide specific descriptions of exposure levels at which specific reproductive effects are noted. Maternal blood lead levels of approximately 30 μg/dl may be associated with a higher incidence of premature delivery and premature membrane rupture, but these observations require confirmation. In adult males, levels of 50 to 80 μg/dl may be sufficient to induce significant spermatotoxic effects, but this effect has not been conclusively demonstrated.

Lead has not been shown to be teratogenic in man, but animal experiments have demonstrated that high levels of lead that are still compatible with life in sexually mature animals interfere with normal reproduction; these studies include assessment of lead effects in both parents. Reduction in offspring number, weight, and survival and an increase in fetal resorption is a consistent finding in rats, mice, and other species over a range of high-level lead exposures. Effects on offspring have been shown to involve the gametotoxic effect of lead on males as well as females in a number of animal species.

At lead levels presently encountered in occupational exposure, no significant cardiovascular effects are discernible. Clinical data for children suffering from chronic lead poisoning resulting in death indicate that extensive myocardial damage occurs. It is not clear that the associated morphological changes are a specific response to lead intoxication. However, in many instances where encephalopathy is present, the electrocardiographic abnormalities disappear with chelation therapy.

There are insufficient data pertaining to the effects of elevated blood lead levels and the incidence of infectious diseases in man to allow the derivation of a dose-response relationship. Neither can a dose-response relationship be defined for the effects of elevated blood lead levels on the gastrointestinal tract, even though colic is usally a consistent early symptom of lead poisoning in adults exposed occupationally and in infants and young children.

1.2.2 **Effects of Lead on the Ecosystem**

As a natural constituent, lead does not usually pose a threat to ecosystems. The redistribution of naturally occurring lead in the environment, however, has now caused some concern that lead may represent a potential threat to the ecosystem. For example, studies have shown a fivefold increase in lead in tree rings during the last 50 years; this accumulation may serve as a useful index of patterns of environmental lead accumulation.

There are also documented effects of lead on domestic animals, wildlife, and aquatic life. Lead poisoning in domestic animals produces varying degrees of derangement of the central nervous system, gastrointestinal tract, muscular system, and hematopoietic system. As is true in man, younger animals appear to be more sensitive than older ones.

Wildlife are exposed to a wide range of lead levels. Toxic effects from ingestion of lead shot have long been recognized as a major health problem in waterfowl. Several species of small mammals trapped along roadways were tested for lead concentrations. All but one of the species living in habitats adjacent to high-volume traffic showed high concentrations of lead. This was especially true in urban areas.

Lead toxicity in aquatic organisms has been observed and studied experimentally. Symptoms of chronic lead poisoning in fish include anemia, possible damage to the respiratory system, growth inhibition, and retardation of sexual maturity.

There is evidence that lead has both harmful and beneficial effects on plants. Plants are exposed to lead through the leaves, stems, bark, or roots, and the extent of the effects depends on the form, amount, and availability of that lead. The morphology of the plant surface plays the major role in determining the type and quantity of material retained by plants. Meteorological factors are also important in determining the fate of lead that comes into contact with plants. Large deposits of inert insoluble metal compounds on the leaves are probably of little consequence to plants, as the most important factor is the solubility of the metal. Thus, because inorganic lead compounds are generally of low solubility, there is little incorporation and accumulation within the leaves of plants.

The majority of studies reporting lead toxicity in plants have been conducted with plants grown in artificial nutrient culture. These studies have promoted the concept that the effects of lead are dependent on a variety of environmental factors, including anions and cations within the plant and in the growth media, and the physical and chemical characteristics of the soil itself. As lead interacts with many environmental factors, specific correlations between lead effects and lead concentrations are extemely difficult to predict.

1.3 EFFECTS OF LEAD ON POPULATIONS

The frequency distribution of blood lead levels in homogeneous human populations has almost invariably been found to be lognormal. Most data sets of homogeneous populations display a geometric standard deviation (GSD) of 1.3 to 1.5. This would roughly correspond, for example, to an arithmetic standard deviation of 5.3 to 8.5 μg/dl at a mean blood lead of 20 μg/dl.

From the lognormal distribution, given a mean blood lead level and estimated GSD, it is possible to predict the percentage of a population whose blood lead levels exceed or fall below a specified value. It is also possible to estimate the probable increase in mean blood lead levels for a population exposed to a specific increases in environmental lead. These two procedures, used together, provide a method by which air quality standards may be chosen to protect the health of the population.

Blood lead levels vary with geographic location. They are lowest in some remote populations, higher in most rural settings, higher still in suburban areas, and highest in inner-city areas. This gradient follows the presumed lead exposure gradient. Blood lead values also vary by age, sex, and race, although in a somewhat more complex fashion. Generally, young children have the highest levels, with little difference noted between sexes at this age. In older segments of the population, after elimination of occupational exposure in lead workers, males still have a higher blood lead than females. Only limited published data are available comparing the blood levels of the various racial and ethnic groups of the population. These data suggest that urban blacks have higher lead levels than whites, with levels in Puerto Ricans frequently being intermediate.

Results of the numerous studies of environmental lead exposures of man have indicated strongly that man does indeed have cumulative uptake from each source to which he is exposed. Equally important, these studies have shown that the blood lead level represents a summation of the absorption from each of these sources.

Data for the two most widespread environmental sources of lead other than food permit summary statements concerning their quantitative relationship with blood lead levels: air and soil/dust. Blood lead levels were found to increase with rising air lead concentrations. The relationships were found to be either log-linear or log-log. Evaluation of the equations at various commonly observed air lead levels revealed that the ratio between changes in blood and changes in air lead varied generally between 1 and 2 and that it was not constant over the range of air exposures. This implies that an increase of 1 μg/m^3 of air lead results in an average increase of 1 to 2 μg/dl in blood lead levels. Suggestive evidence indicates that children may have higher ratios than adults and that males may have higher ratios than females.

One of the most extensive data sets on blood lead in children comes from a study by the U.S. Department of Housing and Urban Development on the blood lead values of approximately 180,000 children in New York City. These data covered the period March 1970 through December 1976. A preliminary analysis of these important research findings was presented to the Subcommittee on Lead of EPA's Science Advisory Board in October 1977. The following patterns appear to be indicated by these data:

1. There is a definite difference in blood lead values for racial and ethnic groups, blacks having higher mean lead levels, and Hispanics and whites having lower levels.
2. Analysis shows that the mean blood lead level is related to race and ethnicity, age, and year of sampling. This age dependence is similar for all years: The 1- to 12-month-old group has the lowest levels, and generally the maximum is found in 2- to 4-year-olds.

3. There was a consistent decrease of mean blood lead levels over the course of the study. This decrease was coincident with a reduction in lead levels in gasoline in the New York City area.
4. There appears to be a likely corresponding decrease in the air lead. However, it should be pointed out that air lead data for New York City are sparse and that it would be unwise to assume that the air lead level as measured at a single location would be the same for all locations. Because of the height of the sampler, it is also questionable whether the air lead level would represent the level to which the population is exposed.

Consistent relationships between blood lead levels and exposure to lead-containing soil have been shown. Also, children exposed to higher concentrations of soil and house dust lead have been shown to have elevated concentrations of lead on their hands. The intermediate link, from elevated hand levels of lead to elevated blood levels, has not yet been established. Quantitatively, blood lead levels have been shown to increase 3 to 6 percent given a doubling of the soil or dust lead content.

Significant water lead exposures in this country have only occurred in places having a soft water supply and using leaded pipes. Such exposures have been shown to be associated with significant elevations of blood lead. They have also been linked to cases of mental retardation.

Exposure to leaded paint still constitutes a very serious problem for American children in urban settings. Although new regulations of the lead content of paint should alleviate the problem in new housing, the poorly enforced regulation and lack of regulation of the past have left a heavy burden of lead exposures. Most of the studies on lead poisoning in children have assumed an association with leaded paint. It is very difficult in these studies to measure the actual amount of exposure. There is nevertheless incontrovertible evidence that the contribution from this source is very significant for certain segments of the population.

Food lead exposures are thought to be a source of a significant portion of blood lead. Precise quantitative estimates of the relationship between food and blood lead are not available, however. Similarly, precise quantitative estimates are not available for the relative contributions of different sources to the total amount of lead in the diet. It is clear, however, that probably the largest proportion of dietary lead is derived from food processing (e.g., from solder in the seams of cans), and some is also derived from lead in the air and the soil.

1.4 ASSESSMENT OF RISK FROM HUMAN EXPOSURE TO LEAD

Of the estimated 160,000 metric tons of lead emitted into the atmosphere in 1975, the combustion of gasoline additives and waste oil accounted for 95 percent of the total. Once lead is introduced into the air, it is subject to a variety of processes, including dry deposition, precipitation, and resuspension.

Other uses of lead result in other avenues of exposure: (1) Lead in paint makes lead available by ingestion; (2) lead in plumbing for potable water where the water is soft (low pH) permits leaching and makes lead available by ingestion; (3) lead in the diet, introduced by processing, packaging, and raw food stock, also makes lead available by ingestion. It is therefore important to realize that human exposure to lead is the summation of all these complex and individual sources.

The factors that govern the quantitative aspects of inhalation and ingestion of lead have been pointed out, and attention has been given to the fact that ingestion includes both food and nonfood materials. In the case of children, the nonfood material has especially important implications. Thus the total internal dose is a function of all external sources with which the body comes into contact. The relative significance of any given exposure source depends on the specific exposure circumstances and certain attributes of the population at risk.

1.4.1 Use of Blood Lead Levels in Risk Assessment

The evidence for increased blood lead levels, the usual accepted indicator of lead exposure, has evolved from studies of both single-source and multiple-source exposures. Studies of single sources of air lead have included both epidemiological and clinical investigations. Clinical data uniformly demonstrate and quantify the actual transfer of lead in air to blood. The epidemiological data are not as definitive, but they are more relevant to the real world and clearly support such a relationship.

Studies concerned with dust and soil lead exposures may be considered jointly, since most studies have not attempted to isolate their relative contributions. Strong evidence exists to show that these sources can be significant determinants of blood lead levels. Furthermore, investigations involving children exposed to lead-contaminated dust have demonstrated lead on the children's hands, providing strong inferential evidence for an oral route of entry.

Lead-based paint is associated with overt clinical intoxication and widespread excess absorption in children. Screening programs in all major urban areas have sought to abate this severe public health problem, but only with limited success. These children represent a particularly high risk group with respect to the incremental lead exposure attributable to direct inhalation of atmospheric lead as well as with respect to the ingestion of dust contaminated by lead from the atmosphere.

Studies centered around primary lead smelters and secondary industrial sources in urban settings have consistently and independently demonstrated a relationship between blood lead levels and these mixed sources. Most characteristics that mediate the relationship between blood lead level and lead exposure have been examined in several studies. Age is certainly a significant factor in determining blood lead levels, particularly in children under 6 years of age. With regard to sex differences, there appear to be none among children, whereas in adults, males generally exhibit higher levels than females. Though one study has reported that black children have higher lead levels than white children, the overall data are too sparse to establish a conclusive relationship. Socioeconomic variables such as income and education, as well as general health status, have not been examined in these studies.

A number of summary statements may be made about the quantitative relationships pertaining to blood lead. The weight of evidence indicates that blood lead levels follow a log-normal distribution with a geometric standard deviation of about 1.3 to 1.5. The log-normal distribution possesses properties that make it of value in arriving at acceptable maximal exposures, since it makes it possible to estimate a proportion of a population whose blood lead levels exceed any specified level.

The increase in blood lead level resulting from an increase in air lead concentration is not constant in magnitude over the range of air lead levels commonly found in the environment. The relationship is dependent on many factors, including rate of current exposure and the history of past exposure. The observed ratios vary from air lead level to air lead level; they are generally between 1 and 2. Evidence suggests that the ratios for children may be higher than those of adults; also it suggests that ratios for males may be higher than those for females.

There is general agreement that blood lead levels begin to increase when soil levels are 500 to 1000 ppm. Mean percent increases in blood lead levels, given a twofold increase in soil lead levels, ranged from 3 to 6; this is remarkably consistent given the divergence of the populations studied.

One of the most important aspects of risk assessment is the evaluation of effects of long-term, low-level, or intermittent exposures. In such circumstances, blood lead levels do not always correlate well with the exposure history. In one clinical study of lead exposure by inhalation, an average air level of 3.2 $\mu g/m^3$ over a period of about 7 weeks was related to a significant rise in blood lead after about 7 weeks. When exposed to clean air, the blood lead levels of these same subjects returned to pre-exposure levels.

1.4.2 Use of Biological and Adverse Health Effects of Lead in Risk Assessment

Lead is not conclusively known to have any biological effect on man that can be considered beneficial. Therefore, any of the biological and adverse health effects on man at this time must be considered from a medical point of view that acknowledges the absence of any health benefit/health cost ratio.

Earlier discussion considered the biological and adverse health effects of lead across the entire range of lead exposures. In risk assessment, the primary focus is on those biological and adverse physiological effects that relate to the general population.

Though the literature dealing with the health effects of lead embraces virtually all of the major organ systems in man, hematological and neurological effects are of prime concern. These effects are summarized in Table 1-1. It should be pointed out that Table 1-1 is a lowest-observed-effects level tabulation; i.e., it lists the lowest blood lead levels at which particular effects have been credibly reported for given subpopulations. Four hematological effects are considered: anemia, inhibition of the enzyme δ-ALAD, urinary δ-ALA excretion, and elevation of free erythrocyte porphyrin (FEP).

Anemia is found in children with and without concomitant iron deficiency. Increased lead intake prompts a more severe anemia. This is of special importance in children 1 to 6 years old of lower socioeconomic status, since this group also has a high incidence of iron deficiency.

The literature relating blood lead levels to a statistically significant reduction in hemoglobin points to a threshold level of 40 $\mu g/dl$ for children and a corresponding value of 50 $\mu g/dl$ for adults. The question of a low-threshold or no-threshold

TABLE 1-1. BLOOD LEAD LEVELS VERSUS LOWEST-OBSERVED-EFFECTS LEVELS

Lowest level for observed effects, μg Pb/dl whole blood	Observed effect	Population group
10	ALAD inhibition	Children and adults
15 to 20	Free erythrocyte porphyrin elevation	Adult females and children
20 to 25	Free erythrocyte porphyrin elevation	Adult males
40	Increased urinary ALA excretion	Children and adults
40	Anemia	Children
40	Coproporphyrin elevation	Adults and children
50	Anemia	Adults
50 to 60	Cognitive (CNS) deficits	Children
50 to 60	Peripheral neuropathies	Adults and children
80 to 100	Encephalopathy symptoms	Children
100 to 120	Encephalopathy symptoms	Adults

level for the inhibitory effect of lead on the enzyme δ-ALAD is overshadowed by the larger issue of the health significance of this observation. In any event, a value of 10 μg/dl blood lead appears to represent a threshold level. Elevation of urinary δ-ALA levels, however, appears to be considered an index of physiological impairment, and the threshold level of this effect is approximately that for anemia in children (i.e., 40 μg/dl). This value seems to apply for both children and adults.

Elevation of erythrocyte porphyrin is better accepted as an indicator of physiological impairment. On the basis of a number of studies, threshold values of blood lead at which erythrocyte protoporphyrin is elevated appear to be 15 to 20 μg/dl for children and adult females and 20 to 25 μg/dl for adult males.

The hematological effects described above are the earliest physiological impairments encountered as a function of increasing lead exposures as indexed by blood lead elevations; as such, those effects may be considered to represent critical effects of lead exposure. Although it may be argued that certain of the initial hematological effects (such as ALAD inhibition) constitute relatively mild, nondebilitating symptoms at low blood lead levels, they nevertheless signal the onset of steadily intensifying adverse effects as blood lead elevations increase. Eventually, the hematological effects reach such magnitude that they are of clear-cut medical significance as indicators of undue lead exposure.

Of even greater concern than early symptoms of lead exposures (i.e., hematological impairments) are the neurologic effects of lead that begin to be encountered as the hematological deficits reach clinical magnitudes. Children are most clearly the population at risk for neurologic effects. The neurologic effects, including both peripheral neuropathies and signs of CNS damage, are first encountered for some children as blood lead levels reach 50 to 60 μg/dl; and they very rapidly intensify in severity as a function of increasing blood lead elevations. Of great medical concern is the very steep upward rise in the risk for permanent, severe neurological damage or death as blood lead elevations approach and exceed 80 to 100 μg/dl in children. Inner city children are of particular concern with respect to the manifestation of lead-induced neurologic deficits, as documented by the evidence discussed in Section 11.5.

Some evidence has recently been advanced that suggests that long-term neurobehavioral deficits may also be induced by *in utero* exposures of human fetuses to lead, as indicated by the apparent higher incidence of postnatal mental retardation among children born of mothers experiencing elevated lead exposure before or during pregnancy. Thus women of childbearing age may be another group at special risk by virtue of the potential *in utero* exposures of fetuses. However, the paucity of information on exact exposures experienced by these mothers and the lack of other confirmatory studies do not allow firm statements to be made about probable threshold lead exposure levels for pregnant women that may induce later neurobehavioral deficits in their children.

It is even more difficult to speak of risk-to-health assessment in terms of threshold levels for effects of lead on reproduction, since the relevant data are sparse. However, in no other aspect of health effects is the potential for deleterious health effects of lead as inherently great as in the area of reproduction and development. In particular, lead crosses the placental barrier, placing the human fetus at direct risk. And such exposure begins at a stage of gestation when neural embryonic development is beginning. Placental transfer, coupled with the fact that an effective blood-brain barrier is not present in human fetus, means that there is effectively a direct path from maternal lead exposure to the fetal nervous system.

Available information suggests that there are several possible consequences to the newborn arising from lead exposure. Premature birth is suggested as being associated with elevated blood lead levels in women, and some impairment in the heme biosynthetic pathway may exist in the newborn children of mothers having elevated blood lead levels.

Much of the discussion above has dealt with relationships between blood lead levels and various biological effects of lead. This discussion was primarily concerned with threshold levels at which health effects of lead are first observed in different population groups. Of additional interest is the proportion of a population exhibiting a health effect at a given blood lead level (i.e., the dose-response curve). Three different assessments of dose-response relationships for hematological effects have been carried out and published. These effects are the inhibition of ALAD, elevation of ALA-U, and elevation of EP levels in the blood. As noted elsewhere in this summary, some question exists concerning the relevance of ALAD inhibition to human health. The other two hematological effects are relevant. Table 1-2 shows ALA-U data from two studies, one published and one done by EPA (see Chapter 13).

TABLE 1-2. ESTIMATED PERCENTAGE OF SUBJECTS WITH ALA-U EXCEEDING 5 mg/liter FOR VARIOUS BLOOD LEAD LEVELS

Blood lead level, μg/dl	Zielhuis estimate, %	Azar et al. estimate, %
10	0	2
20	0	6
30	6	16
40	24	31
50	48	50
60	76	69
70	96	84

Published studies (see Chapter 13) of dose-response relationships also exist for erythrocyte protoporphyrin and are presented in Table 1-3.

TABLE 1-3. ESTIMATED PERCENTAGE OF CHILDREN WITH EP EXCEEDING SPECIFIED CUTOFF POINTS FOR VARIOUS BLOOD LEAD LEVELS

Blood lead level, μg/dl	Zielhuis estimate,[a] %	Roels et al. estimate,[b] %	Piomelli estimate,[c] %
10	0	3	9
20	6	27	11
30	22	73	48
40	37	100	80
50	49	–	–
60	–	–	–
70	–	–	–
80	–	–	–

[a] EP > EP of children with blood lead levels < 20 μg/dl.

[b] EP > 82 μg/dl cells.

[c] EP > 33 μg/dl.

1.4.3 **Populations at Risk**

The concept of "special risk" is defined as a population segment exhibiting characteristics associated significantly higher probability of developing a condition, illness, or other abnormal status as a result of exposure to a given toxic agent. With respect to lead, two such segments of human populations are currently definable: preschool children and unborn fetuses, with pregnant women as the recipient population of concern.

1.4.3.1 PRESCHOOL CHILDREN

There is an impressive body of data that indicates that children are inherently more susceptible to lead by virtue of physiology and that they have a different relationship to exposure sources. These physiological factors include: (1) greater lead intake on a per-unit-body-weight basis; (2) greater net respiratory intake as well as greater net absorption and retention of lead entering the gastrointestinal tract; (3) rapid growth, which reduces the margin of safety against a variety of stresses, including nutritional deficiency; (4) certain incompletely developed defense mechanisms in very young children, such as the blood-brain barrier in newborns; and (5) different partitioning of lead in the bones of children compared to that of adults, with only 60 to 65 percent of the lead body burden occurring in bone, and that fraction probably being more labile than in adults.

An important aspect of the dietary habits of very young children in connection with lead exposure is their normal mouthing activity, such as thumb-sucking or tasting of nonfood objects. Such behavior poses a risk of increased contact with dust and soil contaminated with lead. Clinical evidence also exists to indicate children are at special risk for lead effects. Thresholds for anemia and erythrocyte protoporphyrin elevation are lower for children, and a number of neurological effects appear at lower levels of lead in children than in adults.

1.4.3.2 PREGNANT WOMEN

Considerable evidence indicates that pregnant women are a population segment at risk with respect to lead mainly because of increased risk to the fetus and maternal complications. Lead crosses the placental barrier and does so at an early stage in embryonic development. Although quantitative expressions of this risk cannot be stated, certainly the potential for damage exists.

Pregnancy places a physiological stress on a woman in terms of nutritional states that lead to iron and calcium deficiency, in consequence of which bone lead may be mobilized and the hematopoietic system may be placed at higher risk to lead exposure. In addition, data suggest that elevated blood lead levels in pregnant women may result in increased incidence of premature membrane rupture, placing the mother as well as her newborn in a special risk category.

1.4.3.3 UNITED STATES POPULATION IN RELATION TO PROBABLE LEAD EXPOSURES

With the exception of those living in areas with primary lead smelters, most populations exposed to lead live in urban areas. Residents of the central city are at the highest risk in these urban areas. Therefore, for other than point stationary sources of lead, it is the urban population that is at risk, and in particular, central city residents. Blacks and Hispanics are probably subject to greater exposure to airborne lead because higher proportions of these segments of the population live in urban areas. In the United States in 1970, 149 million persons were reported to live in urban areas, and 64 million in the central cities. These figures include about 12 million children under 5 years of age, with approximately 5 million of these children living in central-city areas. There are an estimated 600,000 children in the United States with blood lead values greater than 40 μg/dl. These values do not result from exposure to airborne lead alone; they also include exposure to leaded paint and lead in food. In view of the narrow margin of safety from currently observed urban blood lead levels, children exposed to an additional increment of lead from the air would be at great risk for adverse health effects.

Of the roughly 3 million U.S. pregnancies per year, inner-city women are estimated to account for 500,000. In view of available data, these women and their unborn children are also at high risk.

2. INTRODUCTION

According to Section 108 of the Clean Air Act of 1970, as amended in June 1974, a criteria document for a specific pollutant or class of pollutants shall

> . . . accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.

Air quality criteria are of necessity based on presently available scientific data, which in turn reflect the sophistication of the technology used in obtaining those data as well as the magnitude of the experimental efforts expended. Thus air quality criteria for atmospheric pollutants are a scientific expression of current knowledge and uncertainties. Specifically, air quality criteria are expressions of the scientific knowledge of the relationships between various concentrations — averaged over a suitable time period — of pollutants in the same atmosphere and their adverse effects upon public health and the environment. Criteria are issued to help make decisions about the need for control of a pollutant and about the development of air quality standards governing the pollutant. Air quality *criteria* are *descriptive*; that is, they describe the effects that have been observed to occur as a result of external exposure at specific levels of a pollutant. In contrast, air quality *standards* are *prescriptive*; that is, they prescribe what a political jurisdiction has determined to be the maximum permissible exposure for a given time in a specified geographic area.

In the case of criteria for pollutants that appear in the atmosphere only in the gas phase (and thus remain airborne), the sources, levels, and effects of exposure must be considered only as they affect the human population through inhalation of or external contact with that pollutant.

Lead, however, is found in the atmosphere primarily as inorganic particulate, with only a small fraction normally occurring as vapor-phase organic lead. Consequently, inhalation and contact are but two of the routes by which human populations may be exposed to lead. Some particulate lead may remain suspended in the air and enter the human body only by inhalation, but other lead-containing particles will be deposited on vegetation, surface waters, dust, soil, pavements, interior and exterior surfaces of housing — in fact, on any surface in contact with the air. Thus criteria for lead must be developed that will take into account all principal routes of exposure of the human population.

This criteria document sets forth what is known about the effects of lead contamination in the environment on human health and welfare. This requires that the relationship between levels of exposure to lead, via all routes and averaged over a suitable time period, and the biological responses to those levels be carefully assessed. Assessment of exposure must take into consideration the temporal and spatial distribution of lead and its various forms in the environment.

This document focuses primarily on lead as found in its various forms in the ambient atmosphere; in order to assess its effects on human health, however, the distribution and biological availability of lead in other environmental media have been considered. The rationale for structuring the document was based primarily on the two major questions of exposure and response. The first portion of the document is devoted to lead in the environment — physical and chemical properties; the monitoring of lead in various media; sources, emissions, and concentrations of lead; and the transport and transformation of lead within environmental media. The latter section is devoted to biological responses and effects on human health and ecosystems. An effort has been made to limit the document to a highly objective analysis of the scientific data base. The scientific literature has been reviewed through March 1977. The references cited do not constitute a complete bibliography but they are hoped to be sufficient to reflect the current state of knowledge on those issues most relevant to the establishment of an air quality standard for lead.

The status of control technology for lead has not been treated. For information on the subject, the reader is referred to appropriate control technology documentation published by the Office of Air Quality Planning and Standards (OAQPS), EPA. The subject of adequate margin of safety stipulated in Section 108 of the Clean Air Act also is not treated here; this topic will be considered in depth by EPA's Office of Air Quality Planning and Standards in documentation prepared as a part of the process of establishing an air quality standard.

3. CHEMICAL AND PHYSICAL PROPERTIES

3.1 ELEMENTAL LEAD

Lead is a gray-white metal of bright luster that, because of its easy isolation and low melting point (327.4°C), was among the first of the metals to be placed in the service of man. Lead was used as early as 2000 B.C. by the Phoenicians, who traveled as far as Spain and England to mine it. Its most abundant ore is galena, in which lead is present as the sulfide (PbS), and from which metallic lead is readily obtained by roasting. The metal is soft, malleable, and ductile; it is a poor electrical conductor, and it is highly impervious to corrosion. This unique combination of physical properties has led to its use in piping and roofing, and in containers for corrosive liquids. By the time of the Roman Empire, it was already in wide use in aqueducts and public water systems, as well as in cooking and storage utensils.

Lead is unique among the toxic heavy metals in that it is relatively abundant in the earth's crust; its abundance is estimated[1] to be more than 100 times that of cadmium and mercury, two other systemic metallic poisons. The great environmental significance of lead is the result both of its utility and of its abundance; lead is produced in far larger quantities than any other toxic heavy metal, with world production exceeding 3.5 million tons per year.[2] The properties of elemental lead (Pb) are summarized in Table 3-1.

TABLE 3-1. PROPERTIES OF ELEMENTAL LEAD

Property	Description
Atomic weight	207.19
Atomic number	82
Oxidation states	+2, +4
Density	11.35 g/cm^3 at 20°C
Melting point	327.4°C
Boiling point	1744°C
Covalent radius (tetrahedral)	1.44 Å
Ionic radii	1.21 Å (+2), 0.78 Å (+4)
Resistivity	21.9 x 10^{-6} ohm/cm

There are eight isotopes of lead: Four are stable and four are radioactive. The average abundances of the stable isotopes and the decay characteristics of the radioactive isotopes are listed in Table 3-2. The stable isotopic compositions of naturally occurring lead ores are not identical, but rather show variations reflecting geological evolution.[3] There is no radioactive progenitor for ^{204}Pb. However, ^{206}Pb, ^{207}Pb, and ^{208}Pb are produced by the radioactive decay of ^{238}U, ^{235}U, and ^{232}Th, respectively. Thus the observed isotopic ratios depend on the U/Pb and Th/Pb ratios of the source from which the ore is derived and the age of the ore deposit. The ^{206}Pb/^{204}Pb isotopic ratio, for example, varies from approximately 16.5 to 21, depending on the source.[4]

TABLE 3-2. ISOTOPES OF LEAD

Isotope	Average abundance, %	Decay mode	Energy, MeV	Half-life
^{204}Pb	1.4	Stable	—	Stable
^{206}Pb	26.3	Stable	—	Stable
^{207}Pb	20.8	Stable	—	Stable
^{208}Pb	51.5	Stable	—	Stable
^{210}Pb	—	β	0.017	22 yr
^{210}Pb	—	α	0.047	22 yr
^{211}Pb	—	β	1.4	36.1 min
^{211}Pb	—	α	0.82	36.1 min
^{212}Pb	—	β	0.36	10.6 hr
^{212}Pb	—	α	0.24	10.6 hr
^{214}Pb	—	β	0.72	26.8 min
^{214}Pb	—	α	0.35	26.8 min

3.2 GENERAL CHEMISTRY OF LEAD

Lead is the heaviest element in Group IVB of the periodic table; this is the group that also contains carbon, silicon, germanium, and tin. Unlike the chemistry of carbon, however, the inorganic chemistry of lead is dominated by the divalent (+2) oxidation state rather than the tetravalent (+4) oxidation state. This important chemical feature is a direct result of the fact that the strengths of single bonds between the Group IV atoms and other atoms generally decrease as the atomic number of the Group IV atom increases.[5] Thus, the average energy of a C-H bond is 100 kcal/mole, and it is this factor that stabilizes CH_4 relative to CH_2. For lead, the Pb-H energy is only approximately 65 kcal/mole, and this is too small to compensate for the Pb(II) → Pb(IV) promotional energy. It is this same feature, of course, that explains the marked difference in the tendencies to catenation shown by these elements. Though C-C bonds are present in literally millions of compounds, lead is not known to form any catenated inorganic compounds.

A listing of the solubilities and physical properties of the more common compounds of lead is given in Appendix B. As can be discerned from those data, most inorganic lead salts are sparingly soluble (e.g., PbF_2, $PbCl_2$) or virtually insoluble ($PbSO_4$, $PbCrO_4$) in water; the notable exceptions are lead nitrate, $Pb(NO_3)_2$, and lead acetate, $Pb(OCOCH_3)_2$. Inorganic lead (II) salts are generally relatively high-melting-point solids with correspondingly low vapor pressures at room temperatures. The vapor pressures of the most commonly encountered lead salts are also tabulated in Appendix B. The decay of lead salts in the atmosphere is discussed in Section 6.2.2.

3.3 ORGANOMETALLIC CHEMISTRY OF LEAD

The properties of organolead compounds (i.e., compounds containing bonds between lead and carbon) are entirely different from those of the inorganic compounds of lead. The Pb-C bond energy is approximately 130 kcal/mole,[6] or twice the Pb-H value cited above. Consequently, the organic chemistry of lead is dominated by the tetravalent (+4) oxidation state. An important property of most organolead compounds is that they undergo photolysis when exposed to light. The physical properties of some of the more important organolead compounds are summarized in Table 3-3.

TABLE 3-3. PROPERTIES OF MAJOR ORGANOLEAD COMPOUNDS

Compound	Formula	Appearance	m.p., C	b.p., C
Tetramethyl lead	$(CH_3)_4Pb$	Colorless liquid	-27.5	110
Tetraethyl lead	$(C_2H_5)_4Pb$	Colorless liquid	-130	82[a]
Tetraphenyl lead	$(C_6H_5)_4Pb$	White solid	223	Decomposes
Hexamethyl lead	$(CH_3)_6Pb_2$	Pale oil	38	Decomposes
Hexaethyl lead	$(C_2H_5)_6Pb_2$	Yellow oil	36	100[b]

[a] At 13 mm pressure.
[b] At 2 mm pressure.

Because of their use as antiknock agents in gasoline and other fuels, the most important organolead compounds are the tetraalkyl compounds tetraethyl lead (TEL) and tetramethyl lead (TML). As would be expected for such nonpolar compounds, TEL and TML are insoluble in water but soluble in hydrocarbon solvents (e.g., gasoline). These two compounds are manufactured in extremely large quantities (Chapter 5) by the reaction of the alkyl chloride with lead-sodium alloy:[7]

$$4NaPb + 4C_2H_5Cl \rightarrow (C_2H_5)_4Pb + 3Pb + 4NaCl$$

The methyl compound, TML, is also manufactured by a Grignard process involving the electrolysis of lead pellets in methylmagnesium chloride:[7]

$$2CH_3MgCl + 2CH_3Cl + Pb \rightarrow (CH_3)_4Pb + 2MgCl_2$$

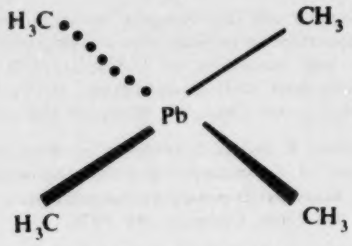
These lead compounds are removed from auto or other internal combustion engines by a process called lead scavenging, in which they react in the combustion chamber with halogenated hydrocarbon additives (notably ethylene dibromide and ethylene dichloride) to form lead halides, usually bromochlorolead. Such inorganic compounds apparently originate as vapors in the combustion chamber of an automobile engine. During their passage through the exhaust system, however, they condense to form small spherical particles with diameters on the order of a few tenths of a micrometer; they also condense or absorb onto the surfaces of co-entrained particles derived from the intake air or from corrosion of the exhaust system. Consequently, lead halides emitted from automobile exhaust are present as vapors, as pure solid particles, and as a coating on the surface of particulate substrates. Mobile source emissions are discussed in detail in Chapter 6 (Section 6.2.2.1).

Several hundred other organolead compounds have been synthesized, and the properties of many of them are reported by Shapiro and Frey.[7] Some of these are used in the commercial preparation of organomercury compounds used as fungicides, and their use as catalysts and stabilizers in industrial processes has been investigated extensively.

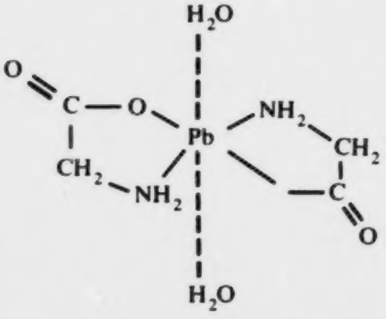
3.4 COMPLEX FORMATION AND CHELATION

The bonding in organometallic derivatives of lead is principally covalent rather than ionic because of the small difference in the electronegativities of lead (1.8) and carbon (2.6). As is the case in virtually all metal complexes, however, the bonding is of the donor-acceptor type, in which both electrons in the bonding orbital originate from the carbon atom.

The donor atoms in a metal complex could, of course, be almost any basic atom or molecule; the only requirement is that a donor, usually called a ligand, must have a pair of electrons available for bond formation. In general, the metal atom occupies a central position in the complex, as exemplified by the lead atom in tetramethyl lead (a), which is tetrahedrally surrounded by four methyl groups. In these simple organolead compounds, the lead is usually present as Pb(IV), and the complexes are relatively inert. These simple ligands, which bind to metal at only a single site, are called monodentate ligands. Some ligands, however, can bind to the metal atom by more than one donor atom, so as to form a heterocyclic ring structure. Rings of this general type are called chelate rings, and the donor molecules which form them are called polydentate (as opposed to monodendate) ligands or chelating agents. In the chemistry of lead, chelation normally involves Pb(11), leading to kinetically quite labile (although highly stable) complexes that are usually six-coordinate. A wide variety of biologically significant chelates with ligands, such as amino acids, peptides, nucleotides, and similar macromolecules, are known. The simplest structure of this type is with the amino acid, glycine, as represented in (b) for a 1:2 (metal: ligand) complex.



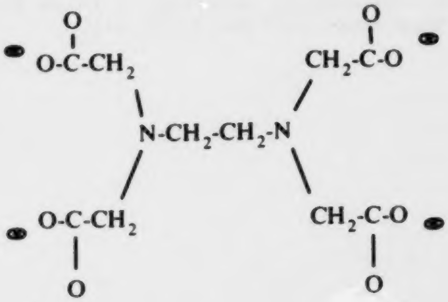
(a)



(b)

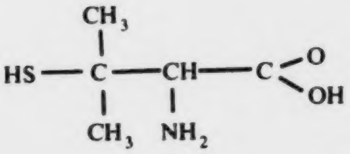
The importance of chelating agents in the present context is their widespread use in the treatment of lead and other metal poisoning.

Since Pb(II) is a relatively soft (or class b) metal ion,[8] it forms strong bonds to soft donor atoms like the sulfur atoms in the cysteine residues of proteins and enzymes; it also coordinates strongly with the imidazole groups of histidine residues and with the carboxyl groups of glutamic and aspartic acid residues. In living systems, therefore, lead atoms bind to these peptide residues in proteins, thereby preventing the proteins from carrying out their functions by changing the tertiary structure of the protein or by blocking the approach by a substrate to the active site of the protein. The role of the chelating agents is to compete with the peptides for the metal by forming stable chelate complexes that can then be transported from the protein and eventually excreted by the body. For simple thermodynamic reasons (see Appendix B), chelate complexes are much more stable than monodentate metal complexes, and it is this enhanced stability that is the basis for their ability to compete favorably with proteins and other ligands for the metal ions. The chelating agents most commonly used for the treatment of



EDTA

(c)



PENICILLAMINE

(d)

lead poisoning are ethylenediaminetetraacetate ions (EDTA) (c), D-penicillamine (d), and their derivatives. EDTA is known to act as a hexadentate ligand toward metals.[9] Recent X-ray diffraction studies have demonstrated that D-penicillamine is a tridentate ligand (binding through S, N, and O) toward cobalt,[10] chromium,[11] and lead,[12] but monodentate toward mercury.[13-15]

It should be noted that both the stoichiometry and structures of metal chelate depend on pH, and that different structures may occur in crystals from those manifest in solution. It will suffice to state, however, that several ligands can be found that are capable of sufficiently strong chelation with lead present in the body under physiological conditions to enable their use in the effective treatment of lead poisoning.

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4. SAMPLING AND ANALYTICAL METHODS FOR LEAD

4.1 INTRODUCTION

Monitoring for lead in the environment, which includes sampling and measurement, is a demanding task that requires careful attention. Lead is receiving careful scrutiny as a pollutant, and the accurate assessment of its impact on the environment is contingent on the acquisition of valid monitoring data. Furthermore, the movement and accumulation of lead in ecosystems occur via complex pathways and compartments. In addition, many difficulties are inherent in the identification and tracing of lead in its various forms in the environment. Airborne lead originates from manmade sources, primarily the automobile, and is extracted from the atmosphere by animals, vegetation, soil, and water. Knowledge of the concentrations of lead in these various media and the movement of lead between and among them is critical for controlling lead pollution and for mitigating the adverse effects of lead in the environment on people.

Sampling and analytical methods for monitoring lead have been devised for almost every purpose. Some methods are too tedious or expensive for general use; others are relatively easily applied but produce results of limited utility or questionable validity; and others are appropriate for use in monitoring lead in certain systems but not in others. The monitoring of environmental lead can be carried out with almost any precision deemed necessary, but actually obtaining precise and accurate results is not a trivial task in many instances. (See Chapter 9 for a discussion of the difficulties in reproducing blood lead analyses.) The primary problem is that of determining what types of monitoring procedures are necessary to realize societal objectives for protecting human health on a practical basis. The objective of this chapter is to review the status of the monitoring procedures available. Another serious problem is the present lack of instrumentation for the continuous analysis of aerosol.

Monitoring for lead involves an operational sequence, based on the scientific method, as shown schematically in Figure 4-1. The type of data to be collected must be defined clearly on the basis of the question(s) to be answered. The required accuracy of the data must be determined and assured by means of a quality assurance strategy for all aspects of the monitoring operation. Similarly, the sampling strategy must be based on the type of data needed and yet take into account requirements imposed by the analytical methods to be used. The selection and application of the analytical methods are in turn influenced by the kind of data needed, the types of samples collected, the analytical capabilities available, and other factors. Ultimately, analysis of the data obtained determines whether the sequence has reached a satisfactory conclusion or if modifications of any particular segments of the sequence are required. Although there are numerous technical sources of information concerning sampling strategy, sampling methods, sample preparation, and analyses, only a few of the most noteworthy are cited here. These include the National Academy of Sciences report on lead,[1] Stern's three-volume compendium on air pollution,[2] the Geological Survey review of lead in the environment,[3] and the National Science Foundation publication, "Monitoring for Lead in the Environment."[4]

In succeeding sections, the specific operations involved in monitoring are discussed. Site selection is treated succinctly because of the dearth of criteria in the literature and the necessity for establishing specific site criteria for each sampling requirement. Much remains to be done toward establishing criteria for location of samplers. The various samplers used to collect lead data are described. Methods for collecting dustfall, water, soil, and vegetation samples are reviewed along with current sampling methods specific for mobile and stationary sources. The processing of samples for analysis is critical and influences the selection of filter materials and characteristics. This is an area of monitoring that is receiving much attention because of the interferences that have been encountered.

The analytical section is lengthy because of the

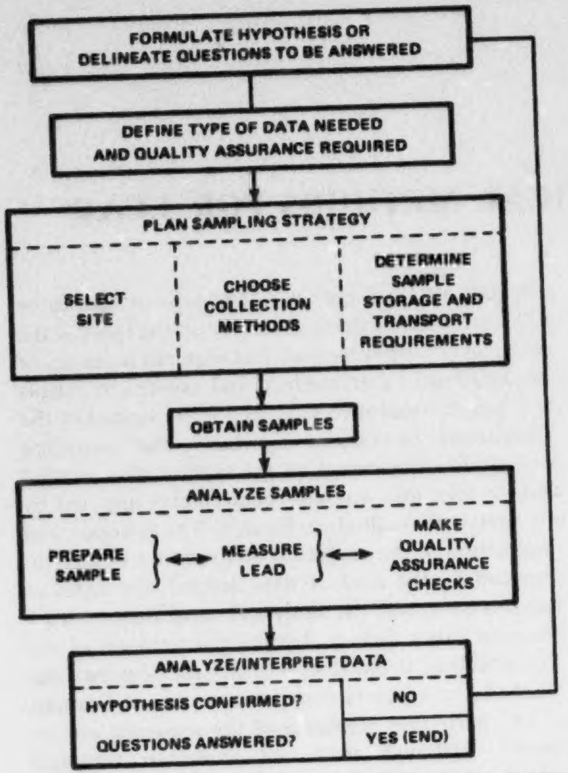
FORMULATE HYPOTHESIS OR DELINEATE QUESTIONS TO BE ANSWERED
DEFINE TYPE OF DATA NEEDED AND QUALITY ASSURANCE REQUIRED
PLAN SAMPLING STRATEGY
SELECT SITE
CHOOSE COLLECTION METHODS
DETERMINE SAMPLE STORAGE AND TRANSPORT REQUIREMENTS
OBTAIN SAMPLES
ANALYZE SAMPLES
PREPARE SAMPLE
MEASURE LEAD
MAKE QUALITY ASSURANCE CHECKS
ANALYZE/INTERPRET DATA
HYPOTHESIS CONFIRMED?
QUESTIONS ANSWERED?
NO
YES (END)

Figure 4-1. Sequence of operations involved in monitoring for lead in the environment.

large variety of methods applied to lead analysis. Analysis is the most advanced area of monitoring operations, and if used properly, analytical methods are already available that are capable of providing all the required data.

4.2 SAMPLING

The purpose of sampling is to obtain lead-containing particles, adsorbed gases, liquids, and solid samples that will provide a measure of the nature and concentration of lead at various points in the environment. Sampling encompasses not only the method of sample collection, but also the selection of sampling sites and procedures applicable to the processing of samples.

4.2.1 **Sampler Site Selection**

The location of sample collection devices has important and pervasive effects on the data obtained. In monitoring ambient air for lead, the proximity to the sampler of mobile and stationary sources is of prime importance. Also of importance are the height of the sampler intake above the ground and the local topography, climate, and lead level in the soil. Ott[5] has enumerated the problems and difficulties encountered in comparing data obtained from air monitoring stations in different cities.

General guidelines for locating ambient air samplers include the following:

1. Samplers should be a uniform height above the ground, although to assess the risk to children, some samplers should also be located at a child's height (2 to 3 ft).
2. Sampler inlets should be at least 3 m from any obstruction.
3. Samplers should be located in areas free of local source influence and convection or eddy currents.

Most existing sampler sites do not meet these criteria, and information on sampler location is not usually provided with data.[5] The number of monitoring sites in an air monitoring network should be related to geography, population, and sources.[6] Since there is no suitable, continuous method for measuring lead in air, the sampling period and frequency are also important in the overall sampling strategy. It should be noted, however, that it is not possible to discuss sampling plans outside the context of a particular objective (e.g., characterization of rural or urban background levels, assessment of health hazards to people, determination of source effects, or delineation of transport mechanisms).[4] The treatment of sampling in detail is outside the scope of this discussion, but reference should be made to the available sources.[6,7]

4.2.2 **Sampling Errors**

The fidelity with which a sample reflects the quantity and nature of lead in any medium being sampled is basic to the obtaining of valid data and therefore to an understanding of the phenomena being investigated. In Section 4.2.1, the importance of site selection for collecting samples of airborne lead was noted. In Section 4.2.6.2, the problems of dilution of samples from mobile sources are noted. A general sampling error associated with sampling of airborne particulates is discussed here.

Most ambient sample collections are obtained nonisokinetically; that is, as the air is drawn into the sampler inlet, the speed and direction of the air are changed. The inertial characteristic of suspended particulates bring about losses of larger particles both by drift from the sampled air stream and by impaction on the surface of the sampler inlet. It has been shown that appreciable errors may result from nonisokinetic sampling, primarily because of the loss of large particles (those with diameters exceeding 10 μm).[8] Generally, it is not possible to estimate the error under any specified conditions. But such errors may be minimized by avoiding eddy formation, turbulence, divergence or convergence, and changes in direction of the sampled air stream.

4.2.3 **Sampling for Airborne Particulate Lead**

Airborne lead is primarily carried by particulates or aerosols, but in smaller concentrations, it may occur in the form of organic gases. Samplers range from the widely used high-volume filter sampler to a variety of other collectors that employ filters, impactors, and impingers.

4.2.3.1 HIGH-VOLUME SAMPLER

The most widely used method for sampling airborne particulates in the 0.1- to 10-μm range is the high-volume air sampler,[9,10] which is routinely used in the National Air Surveillance Networks. The method requires a vacuum cleaner type of air blower that draws air through a filter at rates as high as 2 m^3/min. Since the normal sampling period is 24 hr, particulates from a sample volume of about 2000 m^3 are collected. Because the air flow varies with filter type and the degree of filter loading, it is necessary at least to measure initial and final air flows. Gross particulate loading is determined by carefully weighing the filter before and after sample collection. The lead content is then determined by one of the analytical methods described in the following.

Commercial high-volume samplers in which the filter is held in a horizontal plane and protected from dustfall by a housing are available.[9] An 8- by 10-in. glass fiber filter is usually recommended. Problems with filter selection are discussed in a subsequent section.

High-volume samplers are inexpensive, easy to operate, and in widespread use. A measure of their precision and ease of operation can be deduced from the observation that an interlaboratory relative standard deviation for total particulate collection has been reported of 3.7 percent over the range 80 to 125 μg/m^3. The disadvantages of the high-volume sampler include the lack of separation of particulates by size, the interferences by impurities in the filters with some analytical procedures, and the particle fracturing that occurs on impact, which precludes subsequent determination of size distribution.[9] In addition, high-volume samplers are usually operated nonisokinetically; this results in an underestimation of the airborne concentration of large particles.[11] If there is appreciable mass in particles with aerodynamic diameters greater than about 10 μm, this effect may be important. Isokinetic impactor measurements run in Los Angeles have indicated that the mass median equivalent diameters are apparently larger than those measured under nonisokinetic conditions.[12] This topic is also discussed in Section 6.3.2.1.

An interlaboratory comparison program being conducted in Europe has compared total particulate results from high- and low-volume samplers.[13] Based on the low-volume sampler data, the precision of total particulate collection of the high-volume sampler is estimated at ± 0.5 μg/m^3. Of course, such comparisons apply only to the particular conditions and methodology of sampling and analysis used in that study.

4.2.3.2 DICHOTOMOUS SAMPLER

The size distribution of airborne particulates can be determined by using multistage impactors and impingers or by analyzing unfractionated samples. Such information is desirable for monitoring sources of a pollutant as well as for assessing potential effects of the pollutant on human health. The above techniques are expensive to use on a large scale and generally require extended sampling periods. Measurements[14] have indicated that airborne particulates usually have a bimodal size distribution and also that there is a distinct difference in the effects of small and large particles on humans.[15]

A dichotomous sampler for particulates has been designed to collect and fractionate samples into two size ranges.[16] The dichotomous sampler uses virtual impaction to avoid the particle bounce errors frequently encountered with cascade impactors.[17] Virtual impaction involves the separation of particles into separate air streams by inertial means.[16] In the apparatus, the largest portion of the air stream is pulled through an annular path so that it changes direction, while a small air flow is maintained in a straight path. The inertia of the larger particulates tends to keep them in the straight path while the smaller particles are diverted with the main stream. Two stages of virtual impaction have been used to obtain better fractionation. Membrane filters in the two air paths collect the respective samples. The particle diameter demarcation of the two fractions is normally between 2.0 and 3.5 μm in various designs. Commercial dichotomous samplers are available, but they are considerably more expensive than high-volume samplers.

Tests of a prototype dichotomous sampler in St. Louis indicated[16] that 80 percent of the particulate lead was contained in particles less than 2 μm in diameter, whereas only 20 percent was found to be in larger particles. Other tests to evaluate the performance of dichotomous samplers are under way.[18]

4.2.3.3 TAPE SAMPLER

Though dustfall and high-volume collectors usually require 24 hr sampling periods to obtain a sufficient analytical sample, there may be a need in source and transport studies to monitor airborne particulates for shorter time intervals. The tape sampler draws air through a spot on a filter tape that advances automatically at preset intervals (e.g., every 2 hr).[9] At a sampling rate of about 0.56 m^3/hr (20 ft^3/hr) for a 2-hr interval and with a 2.54-cm (1-in.) spot diameter, it is possible to analyze the collected sample for lead using anodic stripping voltammetry analysis.[19] Atmospheric concentrations of lead ranging from 0.1 to 2.0 $\mu g/m^3$ were measured at monitoring stations in Chicago and Washington using tape samplers.[19] Diurnal cycles in airborne lead concentrations were obtained that correlate with manmade sources of lead.

4.2.3.4 IMPACTORS AND IMPINGERS

Impactors are multistage particulate collection devices designed to provide a number of size fractions. The modified Andersen cascade impactor used in the National Air Surveillance Networks (NASN) is described here.[20] Others are described in standard texts.[2,21]

The cascade impactor fractionates particles in a series of five or six collection stages.[20] Particles pass through a series of jets, 400 per stage, that are progressively smaller. Under each series of jets is a collection plate. The size fraction of particles collected at each stage depends on the air velocity, geometry, and previous stages. The last stage consists of a filter. Air is pumped through the impactor at 0.14 to 0.17 m^3/min by means of an air pump on the downstream side. Aluminum foil is used as the collector, and the size fraction is determined by weighing before and after a 24-hr sample is collected. Five fractions are usually obtained: < 1.1, 1.1 to 2.0, 2.0 to 3.3, 3.3 to 7, and > 7 μm.

Results obtained by the NASN[22] indicate that lead particulates typically have mass median diameters in the range of 0.25 to 1.43 μm. Analysis by optical emission spectrography indicated that for particles less than 0.5 μm in diameter, the lead content was 2 to 4 percent. A cascade impactor has also been applied to multielement size characterization of urban aerosols.[23]

A size-selective particle sampler using cyclones has also been described,[24] and a ten-fraction-size sample can be obtained with the Lundgren impactor.[25]

Impingers collect atmospheric aerosols by impingement onto a surface submerged in a liquid.[2,9] Impactors are sometimes called dry impingers. As in impactors, impingement relies on the inertial characteristics of the particle for collection on a surface. High collection efficiencies for particles as small as 0.1 μm may be obtained in wet impingers.[2]

4.2.4 **Sampling for Vapor-Phase Organic Lead Compounds**

In determining the total quantity of lead in the atmosphere, air is drawn through a membrane or glass filter for collecting particulate lead and then through a suitable reagent or absorber for collection of gaseous compounds that pass through the filter.[26] Since the normal filter used has a nominal 0.45-μm pore size, analysis by this method will include any material that passes through these pores, although it is considered to be primarily organic lead. Organic lead may be collected on iodine crystals, adsorbed on activated charcoal, or absorbed in an iodine monochloride solution.[4] Reviews of the procedures are available.[27,28]

The procedures using iodine monochloride have been described and are claimed to be effective.[26] In one experiment, two bubblers containing the solution were placed in series in the sampling train. Head levels corresponding to about 2.0 $\mu g/m^3$ of organic lead were obtained in the first bubbler, whereas the second gave a blank response, indicating that the collection efficiency of the first bubbler was essentially 100 percent and that the method is quantitative. Analyses were accomplished with atomic absorption spectrometry after chelation of the lead and extraction into an organic solvent. It should be noted, however, that the detection sensitivity was low and that the use of bubblers limits the sample volume.

4.2.5 **Sampling for Lead in Other Media**

In some respects, sampling for lead in water, soil, dustfall, or vegetation can be easier than sampling for airborne lead. However, the sampling conditions may be equally as complex and have a first-order impact on the measurements.

4.2.5.1 WATER

Heavy metals may be distributed in water as ions, as chemical complexes, or as species adsorbed on suspended matter.[4] Methods for sampling and analysis of lead in water have been extensively described.[29,30] Sample containers may be either glass or plastic. The dynamics of the water body should be considered, and defined procedures and precautions should be followed.[4] A variety of procedures, each associated with particular objectives, exists (e.g., separation of dissolved and suspended lead and preservation of water samples to retain their original state).

Analysis of lead in water is typically accomplished with atomic absorption and emission spectroscopy, although analytical methods for other media are also applicable. The natural lead content of lakes and rivers lies in the range of 1 to 10 μg/liter, with an average value of 6.6 μg/liter for North American rivers.[1] Thus, it is commonly found necessary to concentrate the sample by chelating and extracting the lead or by evaporating the water.[3] Techniques for water analysis have been reviewed recently by Fisherman and Erdman.[31]

4.2.5.2 SOIL

Lead in soil samples collected from nearly 1000 locations around the United States ranges from less than 10 to about 700 ppm, with a mean concentration of 16 ppm.[3] Deposition of lead on soil from the atmosphere results in extreme vertical concentration gradients, since lead is relatively immobile in soil.[4] It has been estimated that an average of 1 μg Pb/cm^2· year from rainout or washout or both, and 0.2 μg Pb/cm^2· year from dust accumulates at or near the soil surface.[32] Horizontal gradients of lead concentrations in soil occur as the result of natural and manmade sources. The lead content of soil decreases rapidly with distance from emission sources; for example, reductions of 75 percent are observed in moving from 8 to 32 m from a highway.[33] This point is discussed in detail in Chapter 6.

Soil sampling is not complex.[4] Vegetation and large objects should be avoided, and a representative site should be selected. The vertical integrity of the sample should be preserved and noted. The sample should be air-dried and stored in sealed containers. The sampling should be planned to obtain results representative of the conditions being investigated. Most of the analytical procedures used for airborne particulates are applicable to soils, but the results may not be comparable. Many techniques, including optical emission spectrography, X-ray spectrography, atomic absorption, and the electron microprobe have been used for soil lead analysis.[3] X-ray diffraction has been used to analyze soil samples for lead emitted by automobiles.[34]

4.2.5.3 DUSTFALL

All particles suspended in air are affected by gravitational settling. The settling velocities of larger particles ($\gtrsim$5 to 10 μm) are such that they will be transported shorter distances than the smaller particles ($\lesssim$1 μm), which have nearly negligible settling velocities. Thus dustfall collections can be used to monitor the dispersion of particulate lead from a specific source. The collections are made by placing open containers at appropriate sites free of overhead obstructions.[9,10] Using buckets to measure dustfall can lead to inaccurate data; wind eddies created by the walls of the bucket may greatly affect deposition. The dustfall surface should be smooth and flat, presenting as little disturbance to the wind as possible. These points are discussed by Patterson.[35]

Dustfall is generally reported in units of grams per square meter per month (g/m^2-mo) and may be analyzed by the methods described for particulates collected on filters.[9] The "ASTM Standard Method for Collection and Analysis of Dustfall" provides detailed procedures.[36] One comparison of lead quantities collected by dustfall and by filtration indicated consistently that the lead content of particulates collected by filtration in the high-volume sampler was higher than in dustfall.[37] This is a result primarily of the low settling velocities of the smaller particles, which make up a significant fraction of the total particulate.

4.2.5.4 VEGETATION

Lead analysis of plant tissues has been less extensive than studies in other media. Lead deposited on leaf surfaces by fallout can be removed and analyzed.[38] Lead in plants is usually observed to be less than 1 μg/g dry weight, although levels as high as 31 μg/g have been cited.[1] Plants can absorb soluble lead from soils, but most soil lead is in forms not available to plants.[1] Leafy portions of plants often exhibit higher concentrations of lead, but in general, at least 50 percent of this lead can be removed by washing.[1] Since the presence of lead inside the plants may manifest different effects than that on the plant surface, attempts should be made to differentiate between these two conditions.

Little mention appears in the literature of methods for the field sampling of plant life for environmental studies. The standard methods and procedures usually are focused on statistical sampling for determination of nutrient elements in food crops.

Plant tissue collection and treatment have been reviewed by Skogerboe et al.[4] Sampling of plant materials is generally carried out by random selection of the indigenous species representative of a given area of interest. Where the entire plant is not collected, emphasis is usually placed on the portion of the plant consumed by herbivores or harvested for market. In developing sampling plans, there should be close coordination between plant and animal sampling groups, especially where foodchains are involved.

Before analysis, a decision must be made as to whether or not the plant material should be washed to remove surface contamination from fallout and soil particles. If the plants are sampled in a study of total lead contamination, or if they serve as animal food sources, washing should be avoided. If the effect of lead on plant processes is being studied, or if the plant is a source of human food, the plant samples should be washed. In either case, the decision must be made at the time of sampling, as washing cannot be effectively used after the plant materials have dried. Neither can fresh plant samples be stored for any length of time in a tightly closed container before washing, because molds and enzymatic action may affect the distribution of lead on and in the plant tissues. Freshly picked leaves stored in sealed polyethylene bags at room temperature generally mold in a few days. Storage time may be increased to approximately 2 weeks by refrigeration.

Methods reported in the literature for removing surface contamination vary considerably, ranging from mechanical wiping with a camel-hair brush to leaching in mineral acids or EDTA. Removal of surface contamination with minimum leaching of constituents from leaf tissue can generally be accomplished by using dilute solutions of selected synthetic detergents followed by rinsing in deionized water.

After collection, plant samples should be dried as rapidly as possible to minimize chemical and biological changes. Samples that are to be stored for extended periods of time or to be ground should be oven-dried for at least 4 hr at 70°C to arrest enzymatic reactions and render the plant tissue amenable to the grinding process. Storage in sealed containers is always advisable.

4.2.5.5 FOODSTUFFS

In 1972, lead was included in the Food and Drug Administration Market Basket Survey, which involves nationwide sampling of foods representing the average diet of an 18-year-old male (i.e., the individual who on a statistical basis eats the greatest quantity of food).[39] Various food items from the different food classes are purchased in local markets and made up into meals in the proportion that each food item is ingested; they are then cooked or otherwise prepared as they would be consumed. Foods are grouped into 12 food classes, then composited and analyzed chemically. The quantities represented in the Total Diet Survey and the percentages of these foods grouped in the diet are presented in Table 4-1.

TABLE 4-1. DAILY FOOD INTAKE[39]

		Food consumption	
	Food group	Avg. g/day consumed	% of total diet
I	Dairy products	756	26.1
II	Meat, fish, and poultry	290	9.9
III	Grain and cereal products	369	12.6
IV	Potatoes	204	7.0
V	Leafy vegetables	59	2.0
VI	Legume vegetables	74	2.5
VII	Root vegetables	34	1.2
VIII	Garden fruits	88	3.0
IX	Fruits	217	7.4
X	Oils, fats, and shortening	52	1.8
XI	Sugar and adjuncts	82	2.8
XII	Beverages (including water)	697	24.9
	Total	2922	——

4.2.6 **Source Sampling**

Sources of lead have been well identified and include automobiles, smelters (lead and other nonferrous metals), coal-burning facilities, battery manufacturing plants, chemical processing plants, and facilities for scrap processing and welding and soldering operations. An important secondary source is fugitive dust from mining operations and from soils contaminated with automotive emissions.[34] A complete discussion of sources of lead emissions is given in Chapter 5. The following sections discuss the sampling of stationary and mobile sources, which require different sampling methods.

4.2.6.1 STATIONARY SOURCES

Sampling of stationary sources for lead requires the use of a sampling train at the source to sample the effluent stream. Both particulates and vapors must be collected by the sampling train, and often a probe is inserted directly into the stack or exhaust stream. In the tentative ASTM method for sampling for atmospheric lead, air is pulled through a 0.45-μm membrane filter and an activated carbon adsorption tube.[40] In a study of manual methods for measuring emission concentrations of lead and other toxic materials,[41] use of a filter, a system of impingers, a metering system, and a pump was recommended. The recommended solution in the impingers was nitric acid. More recently, impinger solutions containing iodine monochloride have been shown to be effective.[26]

Since lead in stack emissions may be present in a variety of physical and chemical forms, source sampling trains must be designed to trap and retain both gaseous and particulate lead.

4.2.6.2 MOBILE SOURCES

A variety of procedures has been used to obtain samples of auto exhaust aerosols for subsequent analysis for lead compounds.

In one such procedure, a large horizontal air dilution tube was designed to segregate fine combustion-derived aerosols from larger lead particles ablated from combustion chamber and exhaust deposit.[42] In this procedure, hot exhaust was ducted into a 56-cm-diameter, 12-m-long, air dilution tunnel and mixed with filtered ambient air in a 20-m-diameter mixing baffle in a concurrent flow arrangement. Total exhaust and dilution air flow rate was 28 to 36 m^3/min, which produced a residence time of about 5 sec in the tunnel. At the downstream end of the tunnel, samples of the aerosol were obtained by means of isokinetic probes facing upstream, using filters or cascade impactors. Properly designed air dilution tubes of this type have very few aerosol losses for particles smaller than about 2 μm, the size that can be respired into human lungs.[43]

Air-diluted aerosols from cyclic auto emissions tests have been accumulated in a large plastic bag. Filtration or impaction of aerosols from the bag samples produces samples suitable for lead analysis.[44] Because of the rather lengthy residence time, the bag technique may result in the measurement of anomalously large aerosol sizes because of condensation of low-vapor-pressure organic substances onto the lead particles. This effect may be offset, however, by fallout processes that apply primarily to larger particles (see above).

A low-residence-time sampling system has been used that is based on proportional sampling of raw exhaust, followed by air dilution and filtration or impaction.[45,46] A relatively large sample of aerosol constituents can be obtained because of the high sampling rates of the raw exhaust. Since a constant proportion of the sample flow to the total exhaust flow must be maintained, this technique may be limited by the response time of the equipment to operating cycle phases that cause relatively small transients in the exhaust flow rate.

Most research on aerosol emissions in recent years has used various configurations of the horizontal air dilution tunnel.[42] Several polyvinyl chloride dilution tunnels have been used with good success.[43,47,48] These 46-cm-diameter tunnels of varying lengths have been limited by exhaust temperatures to total flows above approximately 11 m^3/min. Buildup of electrostatic charge on the walls of these plastic systems can cause abnormally high wall losses, but these can be avoided by wrapping the tunnel with a grounded conductive cable at about 30-cm intervals.[47] Similar tunnels have been used in which a centrifugal fan located upstream is used rather than a positive displacement pump located downstream.[43] This geometry produces a slight positive pressure in the tunnel and expedites transfer of the aerosol to holding chambers for studies of aerosol growth. Since the total exhaust plus dilution air flow is not held constant in this system, there may be slight sample disproportionation. However, these errors can be minimized by maintaining a very high dilution air/exhaust flow ratio.[43]

There have also been a number of studies performed using total filtration of the exhaust stream to arrive at material balances for lead using rather low back-pressure metal filters.[45,49-51] The cylindrical filtration unit used in these studies is better than 99 percent effective in retaining lead particles.[51] Supporting data for lead balances generally confirm this conclusion.[52]

Thus a wide variety of sampling and total exhaust filtration procedures have been used to measure the mass emissions of lead compounds from automobiles. Each has its appropriate area of application, depending on the objectives of the various research program carried out. The air dilution tunnel technique is most convenient, is compatible with the usual gas emission measurements, and has therefore been most commonly used.

4.2.7 **Filter Selection and Sample Preparation**

In sampling for lead particulates, air is drawn through filter materials such as fiber glass, asbestos, cellulosic paper, or porous plastics.[2,4] These materials include trace elements that can interfere in the subsequent analysis.[53-55] If the sample is large, then the effects of these trace elements are negligible, but this is not always the case.[56] When samples are prepared for analysis, reduction of the mass of filter material is often accomplished by ashing, either chemically or in an oven.[4] The nature of the filter determines the ashing technique. In other methods of analysis — X-ray fluorescence, for example — analysis can be performed directly on the filter if the filter material is suitable.[16] Because the nature and performance of filter materials are still under investigation, general criteria for their selection cannot be given.[4] A general review of filter materials is available.[57]

The main advantages of glass-fiber filters are their low pressure drop and high particle collection efficiency at high flow rates. The main disadvantage is the variable lead content. In one investigation of Nuclepore filters, examples were given in which the analysis of samples and blanks showed results that did not differ sufficiently to allow use of the data.[4] Others have shown that the variability of residual impurities in some glass filters makes their use inadvisable in most cases,[54,55] and they place a high priority on the standardization of a suitable filter for high-volume samples.[56] Other investigations have indicated, however, that glass-fiber filters are available now that do not present a lead interference problem.[58] The collection efficiencies of filters, and also of impactors, have been shown to be dominant factors in the quality of the derived data.[59] The relative effectiveness of dry ashing (either at low temperatures in an oxygen plasma or at high temperatures) and of wet ashing by acid dissolution is a subject of current concern. Either technique will give good results if employed properly.[4,55]

4.3 ANALYSIS

A variety of useful analytical procedures is available for determination of lead in the environmental samples. The choice of the best method in a given situation depends on the nature of the data required, the type of sample being analyzed, the skill of the analysts, and the equipment available. For general determination of elemental lead, atomic absorption spectroscopy is coming into wider use. However, if multielement analysis is required, and if the equipment is available, X-ray fluorescence has been shown to be capable of rapid, inexpensive analyses.[16] Other analytical methods have specific advantages that call for their continued use in special studies. Only those analytical techniques receiving current use in lead analysis are described in the following. More complete reviews are available in the literature.[3,4,29]

4.3.1 Colorimetric Analysis

Colorimetric or spectrophotometric analysis for lead using dithizone (diphenylthiocarbazone) as the reagent has been used for many years.[60-62] This method is the primary one recommended in a National Academy of Sciences report on lead,[1] and it is the basis of the tentative method of testing for lead in the atmosphere by the American Society for Testing and Materials.[40] Because of its history, it has served as a reference by which other methods have been tested.

Dithizone is an organic compound that reacts with lead salts to form an intensely colored chelated complex. This complex has an absorption maximum, with a known extinction coefficient, at a wavelength of 510 nm, which is the basis of the measurement. Standards can be prepared for calibration purposes by adding known quantities of lead to reagents.

The procedures for the colorimetric dithizone analysis require a skilled analyst if reliable results are to be obtained. The method has been analyzed,[4] and the procedures are given in the literature.[4,40] The American Society for Testing and Materials conducted a collaborative test of the dithizone method[63] and concluded that the ASTM dithizone procedure gave satisfactory precision in the determination of particulate lead in the atmosphere.

The colorimetric dithizone method has the advantage of acceptability by professional organizations. In addition, the required apparatus is simple and relatively inexpensive, the absorption is linearly related to the lead concentration, the method requires only a few micrograms of lead in the sample, large samples can be used, and interferences can be removed.[4] Realization of these advantages depends on meticulous attention to the procedures and reagents. This requires a relatively lengthy procedure and thus a high cost per sample.

4.3.2 Atomic Absorption Analysis

Atomic absorption (AA) spectroscopy is the more generally accepted method for the measurement of lead in environmental sampling.[4] A variety of lead studies using AA analysis have been reported.[26,55,58,64,65]

In AA, the lead determination is made by measuring the resonance absorption of lead atoms. The attenuation of the light beam passing through the sample is logarithmically related to the concentration of the atoms being measured. The lead atoms in the sample must be vaporized either in a precisely controlled flame or in a nonflame medium. The sample solution enters the flame through a nebulizer. The lead absorption wavelengths are precisely at 217.0 nm and 283.3 nm. These wavelengths are produced in a hollow cathode lamp containing lead. The light beam, after passing through the flame, is separated in a monochromator and detected with a photomultiplier. AA requires frequent use of calibration standards to obtain precision and accuracy. Typical precision is 1 to 5 percent. Several hundred samples can be analyzed in an 8-hr day if sample preparation procedures are simple.

In an analysis using AA and high-volume samplers, atmospheric concentrations of lead were found to be 0.63 ± 0.30 ng/scm at the South Pole.[64] Lead analyses of 995 particulate samples from the NASN were accomplished by AA to an indicated precision of 11 percent, with a 0.15 $\mu g/m^3$ detection limit.[58]

Atomic absorption requires as much care as other techniques to obtain highly precise data. Background absorption, chemical interferences, background light losses, and other factors can cause errors. A major problem with AA is that it has become so popular that untrained operators are using it in many laboratories. But for general purposes, AA is the most readily applicable of any of the analytical methods.

Techniques for AA are still evolving, and improved performance involving nonflame atomization systems, electrode-less discharge lamps, and other equipment refinements and technique developments are to be expected.[4]

4.3.3 Anodic Stripping Voltammetry

Electroanalytical methods of microanalysis based on electrochemical phenomena are found in a variety of forms.[66,67] They are characterized by a high degree of sensitivity, selectivity, and accuracy derived from the relationships between current, charge, potential, and time for electrodes in solutions. The electrochemistry of lead is based primarily on the plumbous ion, which behaves reversibly in ionic solutions and has a reduction potential near -0.4 volt versus a standard calomel electrode.[4] Voltammetry, the electrometric method with greatest sensitivity for lead, is discussed here. Other methods are described in the references cited above.

Anodic stripping voltammetry (ASV) describes the process by which the component of interest, lead, is selectively deposited on an electrode by reduction in order to concentrate the component.[66] The working electrode may be a mercury film on a wax-impregnated graphite electrode. After all of the lead in solution is reduced onto the electrode, the analysis involves a stripping process. In this, the lead is oxidized by means of a linearly variable voltage that is applied to the electrode. The voltammogram, a plot of current versus voltage, shows a peak corresponding to the oxidation of the lead. The area of the peak corresponds to the quantity of lead ions available at the stripping voltage.

ASV was applied to the analysis of lead in 2-hr samples obtained with a spot tape sampler.[19] Between 80 ng and 2.4 μg of lead was present in the samples. The average standard deviation obtained in the lead measurements was 5.9 percent. A detailed procedure for sample preparation and analysis has been published.[19]

Voltammetry was also used in analysis of particulate lead collected by an impactor from the ambient atmosphere.[68] Lead concentrations found were in the 600- to 3000-ng/m^3 range.

Current practice with commercially available ASV equipment allows lead determination at the 1 ppb level with routine 5- to 10-percent relative precision.[4] Extension to 0.1-ppb levels is attainable with modified techniques.

Differential ASV[69] and differential-pulsed ASV[70] are reported to give improved sensitivity and to facilitate more rapid analysis, thus lowering the cost.

4.3.4 Emission Spectroscopy

Optical emission spectroscopy has been used to determine the lead content of soils, rocks, and minerals at the 5- to 10-ppm level with a relative standard deviation of 5 to 10 percent;[62] this method has also been applied to the analysis of a large number of air samples.[58,71] The primary advantage of this method is that it allows simultaneous analysis for a large number of elements in a small sample of the material.

Emission spectroscopy essentially consists of observing the optical emission spectra of material excited in a spark, arc, or flame. The wavelength and intensity of the characteristic emission wavelengths of the elements provide both qualitative and quantitative data on composition. Before 1960, the emission spectrometer was the most common instrument in trace-detection laboratories.[72]

When used for a single element such as lead, emission spectroscopy is at a disadvantage because of the expense of the equipment, the required special operator training, and the use of photographic film in the detection process.[4] In a study of environmental contamination by automotive lead, sampling times were much reduced by using a sampling technique in which lead-free porous graphite was used both as the filter medium and the electrode in the spectrometer.[70,73] Lead concentrations of 1 to 10

$\mu g/m^3$ could be detected after a half hour flow at 800 to 1200 ml/min through the filter.

Scott et al. analyzed composited particulate samples obtained with high-volume samplers for about 24 elements, including lead, using a direct-reading emission spectrometer.[74] Over 1000 samples collected by the NASN in 1970 were analyzed. Careful consideration of accuracy and precision led to the conclusion that optical emission spectrometry is a rapid and practical technique for analysis of particulates.

4.3.5 Electron Microprobe

When an intense electron beam is incident on a material, it produces, among other forms of radiation, X rays whose wavelengths depend on the elements present in the material and whose intensity depends on the relative quantities of these elements. This X-radiation is the basis of the electron microprobe method of analysis. An electron beam that gives a spot size as small as 0.2 μm is possible. The microprobe is often incorporated in a scanning electron microscope that allows precise location of the beam. Under ideal conditions, the analysis is quantitative, with an accuracy of 1 to 3 percent. The mass of the analyzed element may be in the 10^{-14} to 10^{-16} g range.[75]

Ter Haar and Bayard[76] applied the electron microprobe method to the analysis of the composition of airborne lead-containing particles. Particles collected on membrane filters were mounted on special substrates and analyzed for lead compounds.[76] The analysis was based on the ratios of elemental X-ray intensities. From an environmental monitoring viewpoint, the ability to determine the composition of complex lead particulates with high precision was demonstrated. The percentage composition of lead compounds in the sample ranged from a low of 0.1 percent to a high of over 37 percent.

Electron microprobe analysis is not a widely applicable monitoring method. It requires expensive equipment, complex sample preparation, and a highly trained operator. The method is unique, however, in providing composition information on individual lead particles, thus permitting the study of dynamic chemical changes and perhaps allowing improved source identification.

4.3.6 X-Ray Fluorescence

X-ray fluorescent emissions that characterize the elemental content of a sample occur when atoms are irradiated at sufficient energy to remove an inner-shell electron.[4] This fluorescence allows simultaneous identification of a range of elements, including lead. For example, 22 elements were identified and quantitatively analyzed in particulate samples from dichotomous samplers without intermediate sample preparation.[16] This analytical method is identical to that described for the electron microprobe in the preceding section but utilizes different excitation sources.

X-ray fluorescence requires a high-energy irradiation source. X-ray tubes,[16,23] electron beams,[75] and radioactive isotope sources[77] have been used extensively.[78,79] To reduce background, secondary fluorescers have been employed.[16] The fluorescent X-ray emission from the sample may be analyzed with a crystal monochromator and detected with scintillation, with proportional counters,[4] or with low-temperature semiconductor detectors that discriminate the energy of the fluorescence. The latter technique requires a very low level of excitation.[16]

X-ray emission induced by charged-particle excitation (proton-induced X-ray emission, or PIXE) offers an attractive alternative to the more common techniques.[80-82] Recognition of the potential of heavy-particle bombardment for excitation occurred in 1970, and an interference-free sensitivity down to the picogram range was demonstrated.[80] The excellent capability of accelerator beams for X-ray emission analysis is partially due to the relatively low background radiation associated with the excitation. The main contribution is Bremsstrahlung from secondary electron emission. The high particle fluxes obtainable from accelerators also contribute to the sensitivity of the PIXE method. Literature reviews[83-86] on approaches to X-ray elemental analysis agree that protons of a few MeV energy provide a preferred combination for high sensitivity analyses under conditions less subject to matrix interference effects. As a result of this premise, a system designed for routine analysis has been described,[81] and papers involving the use of PIXE for aerosol analysis have recently appeared.[81,82]

Advantages of X-ray fluorescence methods include the ability to detect a variety of elements, the ability to analyze with little or no sample preparation, and the availability of automated analytical equipment. Disadvantages include the need for low blank filters, expensive equipment, liquid nitrogen (e.g., for energy-dispersive models, and highly trained analysts. The detectability level for lead is about 20 ng/cm² of filter area, which is well below the quantity obtained in normal sampling periods with the dichotomous sampler.[16]

4.3.7 Methods for Compound Analysis

Colorimetry, atomic absorption, and anodic stripping voltammetry are restricted to measurement of total lead and thus cannot identify the various compounds of lead. The electron microprobe and other X-ray fluorescence methods provide approximate data on compounds on the basis of the ratios of elements present.[76] Gas chromatography using the electron capture detector has been demonstrated to be useful for organic lead compounds.[28] Powder X-ray diffraction techniques have been applied to the identification of lead compounds in soil.[34]

4.4 CONCLUSIONS

To monitor lead aerosol in air, sampling with the high-volume sampler and analysis by atomic absorption spectrometry have emerged as the most widely used method. Sampling in this way does not provide for fractionation of the particles according to size, nor does it allow determination of the gaseous (organic) concentrations; these capabilities may prove important for special studies. The size distribution of lead aerosol is important in considering questions regarding exposure by inhalation; sampling with cascade impactors or dichotomous samplers is necessary to such evaluations. To determine gaseous lead, it is necessary to back the filter with chemical scrubbers or a crystalline iodine trap.

X-ray fluorescence and optical emission spectroscopy are applicable to multielement analysis and are convenient to apply to the measurement of lead in such studies. Because of the many environmental variables implicit in site monitoring, the development of useful biological monitoring techniques may be of more direct utility.

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5. SOURCES AND EMISSIONS

5.1 NATURAL SOURCES

Lead enters the biosphere from lead-bearing minerals in the lithosphere through both natural and human-mediated processes. Measurements of surface materials taken at 8-in. depths in the continental United States[1] show a median lead concentration of 15 ppm. Ninety-five percent of these measurements show 30 ppm of lead or less, with a maximum sample concentration of 700 ppm. In natural processes, lead is first incorporated in soil in the active soil zone, from which it may be absorbed by plants, leached into surface waters, or eroded into windborne dusts.[2-5] In addition, minute amounts of radioactive ^{210}Pb reach the atmosphere through the decay of radon gas released from the earth.[6]

Because lead has been used for centuries, it is difficult to determine the range of natural background levels. Calculations of natural contributions using geochemical information, however, indicate that natural sources contribute a relatively small amount of lead to the environment. For example, if the typical 25 to 40 μg/m^3 or rural airborne particulate matter were derived from surface materials containing 15, and rarely more than 30, ppm lead as cited above, then the natural contribution to airborne lead would range from 0.0004 to 0.0012 μg/m^3. In fact, levels as low as 0.0012 to 0.029 μg/m^3 have been measured at a site in California's White Mountains.[7] In contrast, however, annual average lead concentrations in urban suspended particulate matter[8] range as high as 6 μg/m^3. Clearly, therefore, most of this urban particulate lead stems from man-made sources.

5.2 MAN-MADE SOURCES

5.2.1 Production

Lead occupies an important position in the U.S. economy, ranking fourth among the nonferrous metals in tonnage used. The patterns of its flow through industry are identified in Figure 5-1.[9] Approximately 85 percent of the primary lead produced in this country is from native mines,[10] where it is often associated with minor amounts of zinc, cadmium, copper, bismuth, gold, silver, and other minerals.[10] Missouri ore deposits account for about 80 percent of the domestic production.

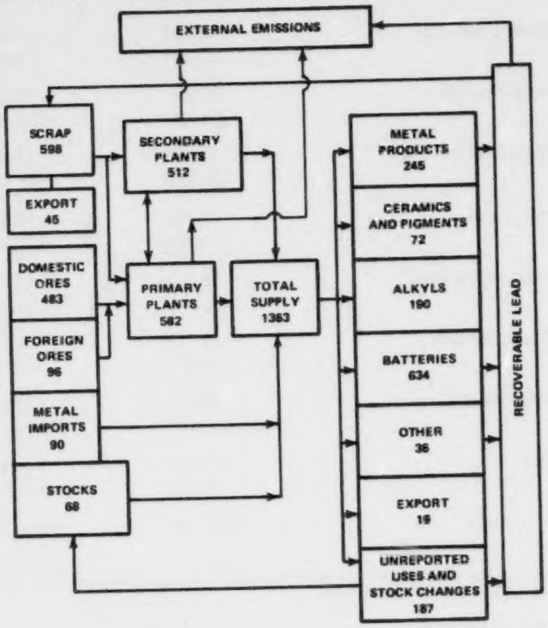


Figure 5-1. Approximate flow of lead through U.S. industry in 1975, metric tons.[9]

5.2.2 Utilization

The reported uses of lead, listed by major product categories in Table 5-1,[11] stood at nearly 1.2 million MT in 1975, with an estimated consumption for 1976 of 1.35 million MT.[12]

Certain products, especially batteries, cables, plumbing, weights, and ballast, contain lead that is economically recoverable as secondary lead. This reserve of lead in use is estimated at 3.8 million MT, of which about 0.6 million MT is recovered annually. Lead in pigments, gasoline additives, ammunition, foil, solder, and steel products is widely dispersed and therefore is largely unrecoverable.

TABLE 5-1. U.S. CONSUMPTION OF LEAD BY PRODUCT CATEGORY[11]
(MT/yr)

Product category	1971	1972	1973	1974	1975
Storage batteries	616,581 (679,803)[a]	661,740 (729,592)	697,888 (769,447)	772,656 (851,881)	634,368 (699,414)
Gasoline antiknock additives	239,666 (264,240)	252,454 (278,340)	248,890 (274,410)	227,847 (251,210)	189,369 (208,786)
Pigments and ceramics	73,701 (81,567)	80,917 (89,214)	98,651 (108,766)	105,405 (116,213)	71,718 (79,072)
Ammunition	79,423 (87,567)	76,822 (84,699)	73,091 (81,479)	78,991 (87,090)	68,098 (75,081)
Solder	63,502 (70,013)	64,659 (71,289)	65,095 (71,770)	60,116 (66,280)	52,011 (57,344)
Cable coverings	47,998 (52,920)	41,659 (45,930)	39,006 (43,005)	39,387 (43,426)	20,044 (22,099)
Caulking lead	27,204 (29,993)	20,392 (22,483)	18,192 (20,057)	17,903 (19,739)	12,966 (14,296)
Pipe and sheet lead	41,523 (45,781)	37,592 (41,447)	40,529 (44,685)	34,238 (37,749)	35,456 (39,092)
Type metal	18,876 (20,812)	18,089 (19,944)	19,883 (21,922)	18,608 (20,516)	14,703 (16,211)
Brass and bronze	18,180 (20,044)	17,963 (19,805)	20,621 (22,735)	20,172 (22,240)	12,157 (13,404)
Bearing metals	14,771 (16,285)	14,435 (15,915)	14,201 (15,657)	13,250 (14,609)	11,051 (12,184)
Weight ballast	15,830 (17,453)	19,321 (21,302)	18,909 (20,848)	19,426 (21,418)	18,156 (20,018)
Other	41,128 (45,345)	43,803 (48,294)	42,110 (46,428)	42,680 (47,056)	36,368 (40,097)
Total	1,298,383 (1,431,514)	1,349,846 (1,488,254)	1,397,876 (1,541,209)	1,450,679 (1,599,427)	1,176,465 (1,297,098)

[a] Short tons/yr given in parentheses.

5.2.3 **Emissions**

Lead or its compounds may enter the environment at any step during its mining, smelting, processing, use, or disposal. Recent estimates of the dispersal of lead emissions into the environment by principal sources indicate that the atmosphere is the major initial recipient. Estimated lead emissions to the atmosphere in 1975 are shown in Table 5-2.

Mobile and stationary sources of lead emissions, although found throughout the nation, tend to be concentrated in areas of high population density, with the exception of smelters. Figure 5-2 shows the approximate locations of major lead mines, primary smelters, alkyl lead plants, and manufacturers of lead storage batteries.[13]

5.2.3.1 MOBILE SOURCES

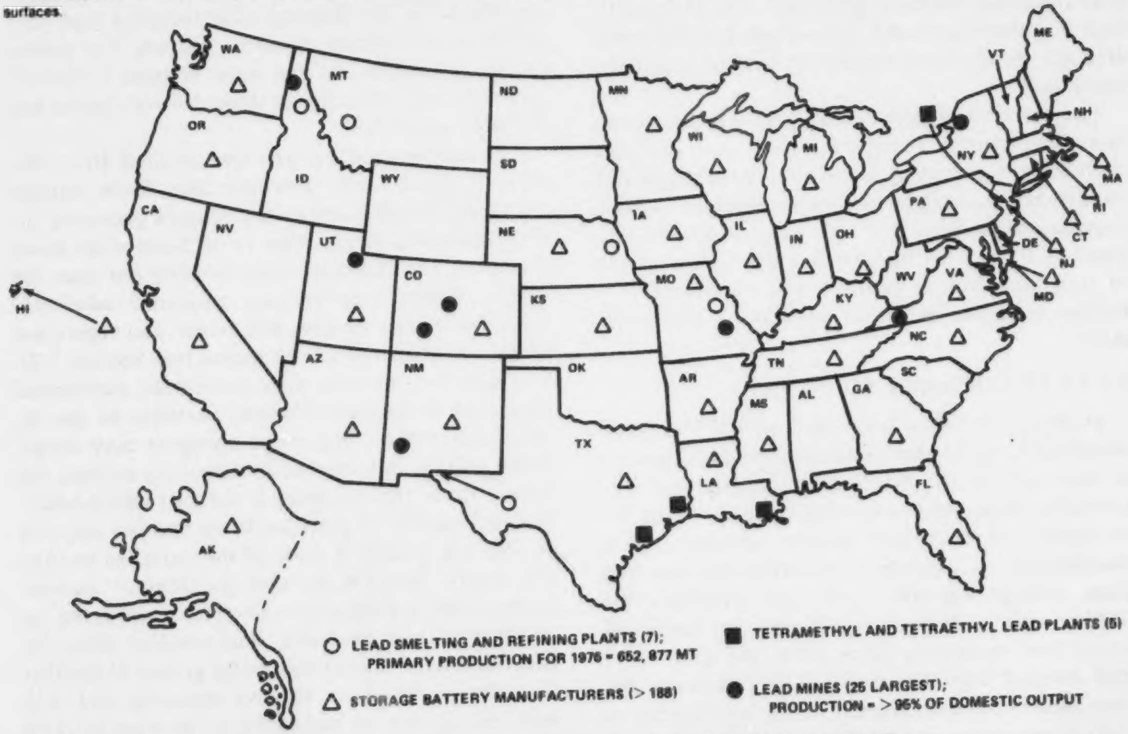
The largest source, by far, of lead emissions to the atmosphere is the exhaust of motor vehicles powered by gasoline that contains lead additives.[14] These mobile-source emissions collectively constitute an estimated 88 percent of total lead emissions (Table 5-2).[9] Other mobile sources, including aviation usage of leaded gasoline and diesel and jet fuel combustion, contribute insignificant lead emissions to the atmosphere.

Lead particulates emitted in automotive exhaust may be divided into two size classes. Particles initially formed by condensation of lead compounds in the combustion gases are quite small in size (well under 0.1 μm in diameter). Particles in this size category that become airborne can remain suspended in the atmosphere for long periods and thus can travel substantial distances from the original sources. Larger particles are also formed as a result of agglomeration of smaller condensation particles.

TABLE 5-2. ESTIMATED ATMOSPHERIC LEAD EMISSIONS FOR THE UNITED STATES, 1975[9,a]

Source category	Annual emissions, MT/yr	Emissions as percentage of Subtotal	 Total
Mobile subtotal	142,000	100	—
Gasoline combustion	142,000	100	88.1
Stationary subtotal	19,225	100	—
Waste oil combustion	10,430	54.3	6.5
Solid waste incineration	1,630	8.5	1.0
Coal combustion	400	2.1	0.2
Oil combustion	100	0.5	0.1
Gray iron production	1,079	5.6	0.7
Iron and steel production	844	4.4	0.5
Secondary lead smelting	755	3.9	0.4
Primary copper smelting	619	3.2	0.4
Ore crushing and grinding	493	2.5	0.3
Primary lead smelting	400	2.1	0.2
Other metallurgical	272	1.4	0.2
Lead alkyl manufacture	1,014	5.3	0.6
Type metal	436	2.3	0.3
Portland cement production	313	1.6	0.2
Pigments	112	0.6	0.1
Miscellaneous	328	1.7	0.2
Total	161,225	—	100

[a] Inventory does not include emissions from exhausting workroom air, burning of lead-painted surfaces, welding of lead-painted steel structures, or weathering of painted surfaces.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○ LEAD SMELTING AND REFINING PLANTS (7); PRIMARY PRODUCTION FOR 1976 = 652, 877 MT
△ STORAGE BATTERY MANUFACTURERS (> 188)
■ TETRAMETHYL AND TETRAETHYL LEAD PLANTS (5)
● LEAD MINES (25 LARGEST); PRODUCTION = > 96% OF DOMESTIC OUTPUT

Figure 5-2. Location of major lead operations in the United States, 1976.[13]

These larger particles, which may be tens of micrometers or larger in diameter, behave in the atmosphere like the larger lead particulates emitted from most stationary sources and fall to the ground in the vicinity of the traffic producing them. The distribution of lead exhaust particles between the smaller and larger size ranges appears to depend on a number of factors, including the particular driving pattern in which the vehicle is used and its past driving history (Chapter 6). But as an overall average, it has been estimated[15] that during the lifetime of the vehicle, approximately 35 percent of the lead contained in the gasoline burned by the vehicle will be emitted as fine particulate, and approximately 40 percent will be emitted as coarse particulate. The remainder of the lead consumed in gasoline combustion is deposited in the engine and exhaust system. Engine deposits are, in part, gradually transferred to the lubricating oil and removed from the vehicle when the oil is changed. Moreover, some oils and lubricants contain lead naphthenate as a detergent. The fate of spent oil and its lead content is of considerable importance. A measure of its significance is reflected in the waste oil combustion values in Table 5-2. In addition, some of the lead deposited in the exhaust system gradually flakes off, is emitted in the exhaust as extremely large particles, and rapidly falls into the streets and roads where it is incorporated into the dust and washed into sewers or onto adjacent soil.

The use of lead additives in gasoline, which was increasing in total volume for many years, is now decreasing as cars designed to use lead-free gasoline constitute a growing portion of the total automotive population (see Section 7.1.1). Regulations promulgated by EPA[16] that limit the average concentration of lead additives in gasoline will contribute to a further reduction in future automotive lead emissions.

5.2.3.2 STATIONARY SOURCES

As shown in Table 5-2 (based on 1975 emission estimates[9]), solid waste incineration and combustion of waste oil are the principal contributors of lead emissions from stationary sources, accounting for two-thirds of stationary source emissions. The manufacture of consumer products such as lead glass, storage batteries, and lead additives for gasoline also contributes significantly to stationary source lead emissions. Since 1970, the quantity of lead emitted from the metallurgical industry has decreased somewhat because of the application of control equipment and the closing of several plants, particularly in the zinc and pyrometallurgical industries.

A new locus for lead emissions emerged in the mid-sixties, however, with the opening of the "Viburnum Trend" or "New Lead Belt" in southeastern Missouri. The presence of seven mines and two accompanying lead smelters in this area makes it the largest lead-producing district in the world and has moved the United States into first place among the world's lead-producing nations. An extensive study to assess the impact of the expanding lead industry in Missouri and to stimulate new emission control technology has been initiated.[17]

Although some contamination of soil and water occurs as a result of such mechanisms as leaching from mine and smelter wastes, quantitative estimates of the extent of this contamination are not available. Spillage of ore concentrates from open trucks and railroad cars, however, is known to contribute significantly to contamination along transportation routes. For example, along two routes used by ore trucks in southeastern Missouri, lead levels in leaf litter ranged from 2000 to 5000 μg/g at the roadway, declining to a fairly constant 100 to 200 μg/g beyond about 400 ft from the roadway.[17]

Another possible source of land or water contamination is the disposal of particulate lead collected by air pollution control systems. The potential for impact on soil and water systems of the disposal of dusts collected by these control systems has not been quantified.

The lead-containing particles emitted from stationary sources occur in various sizes. Those emitted from uncontrolled stationary sources generally include particles larger than 1- to 2-μm mass mean diameter, and therefore tend to settle out near the source. These large-particle emissions add considerable lead to the dust, soil, water, and vegetation in the neighborhood of the source (see Section 7.2). Uncontrolled sources also contribute substantial quantities of smaller-diameter particles to the atmosphere, where long-range transport may occur. When controls are applied to stationary sources, the total mass of the emissions is reduced significantly. But the number of particles being emitted may not be affected greatly if most of the particles emitted are small, because current particulate control methods are usually more effective in removing the larger-diameter particles. The smaller-diameter particles (below 2 μm) may be far greater in number than the larger, more massive particles; and with diminishing size, an increasing proportion is likely to escape collection. Generally, control methods are applied to emissions from stacks, vents, and other process outlets. But lead-containing particles may also be emitted as fugitive dusts in the larger size range (>2-μm diameter) from less controllable sources such as windows and doors, conveyors, and waste piles. Available emission inventories do not include emissions from the exhaust of workroom air, burning of lead-painted surfaces, weathering of lead-painted surfaces, etc. The magnitude of emissions from these sources is unknown.

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6. TRANSFORMATION AND TRANSPORT

6.1 INTRODUCTION

The circulation of lead in the environment (shown conceptually in Figure 6-1) illustrates that lead released into the atmosphere can be delivered to man (animals) via several routes. At present, it is possible to obtain only qualitative or semiquantitative estimates of the movement of lead within and among the various environmental media. This is largely because the physical and chemical transformations occurring within the lead cycle are not well understood. The purpose of this chapter is to summarize the available data that reflect what is known about the transformation and transport mechanisms controlling the distribution and fate of lead in the environment in its various chemical forms. Primary emphasis is placed on the atmosphere, since it serves as the principal medium for transport of lead from manmade sources.

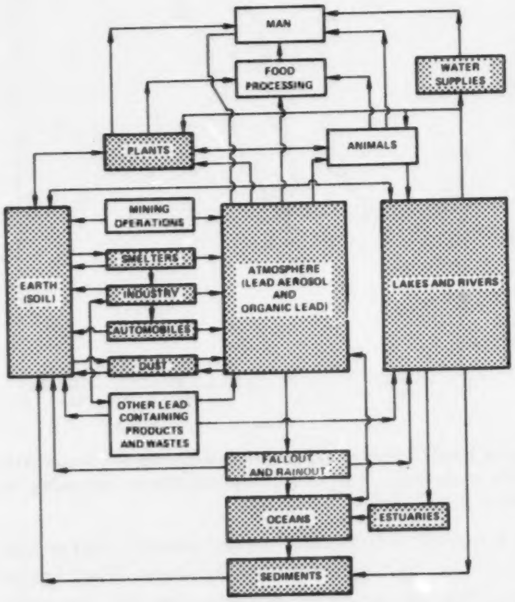

Figure 6-1. Simplified ecologic flow chart for lead showing principal cycling pathways and compartments.

6.2 PHYSICAL AND CHEMICAL TRANSFORMATIONS IN THE ATMOSPHERE

Although lead is introduced into the atmosphere primarily in the particulate form, relatively small amounts are also emitted in the vapor phase. Once lead is introduced into the atmosphere, important physical and chemical changes occur before its transfer to other environmental media. The discussion of these changes will be divided into mobile and stationary source categories. This division is somewhat arbitrary in that the pollutants from both source categories are well mixed in the atmosphere. In those cases in which one type of source predominates (e.g., freeways or smelters), the approach should be reasonably realistic.

6.2.1 Physical Transformations

6.2.1.1 SIZE DISTRIBUTION OF PARTICLES FROM MOBILE SOURCES

Automotive exhaust is the primary source of particulate lead introduced ubiquitously into the atmosphere in urban areas. The size of the particles emitted may range from a few hundredths of a micrometer in diameter to several millimeters, depending on the operating mode, age of exhaust system, fuel lead content, speed and load, acceleration, deceleration, engine condition, and other factors.

Numerous environmental processes, including transformation, transport, deposition, and mechanisms of impact, are prominently influenced by the particle sizes. It is significant, for example, that the sizes of the particles directly affect the probability of lead's being transported via the respiratory system. Because of the importance of lead particle sizes in relation to numerous environmental questions, the size distributions of those particles emitted from automobiles have been studied by many investigators.[1-10]

Figure 6-2 shows the results of a series of variable speed tests made by Hirschler and Gilbert[4] on an auto after about 25,000 miles of deposit accumulation in the exhaust system. The data demonstrate that smaller lead particles make up the largest fraction of those exhausted, and that there is significant exhaust system accumulation of lead particles in both size categories under city-driving conditions. During acceleration, release of these accumulations is quite rapidly induced, but the increased emission drops off during the period of constant highway speed. The effect of speed on the particle size distribution shown in Figure 6-3, as found by Ganley and Springer,[3] also demonstrates that the mean particle sizes emitted decrease with increasing speed. The results of these two studies imply that although larger lead particles are most likely to be deposited in the exhaust system, the deposits are released by ablative processes that cause decreases in particle size. Figure 6-4 compares size distributions at receptor sites in California with those typical of undiluted auto exhaust. The smaller sizes at the receptor sites reflect the decrease in the mean size caused by gravitational settling and other scavenging processes that occur during atmospheric transport. Figure 6-5 compares differential mass distributions at the California receptor sites with those at a freeway site. These distributions are generally bimodal, indicating that particulate lead in the atmosphere may consist of lead emitted by autos and lead that has been deposited on surfaces (soil) and re-entrained via atmospheric turbulence (fugitive dust); or the bimodal distribution may reflect emission patterns. The results of these studies generally indicate that more than half of the lead particles are typically less than 1 µm in diameter, but these estimates may be biased by the failure to use isokinetic sampling techniques (see Section 4.2.3.1).

Lee et al.[9] measured the concentrations and size distributions of particulate emissions from automobile exhaust and found that 95 percent of the total particulate lead was in particles with mass median equivalent diameters (MMED) less than 0.5 µm. All samples were taken at steady-cruise conditions and thus do not represent the typical discharge of particles under wide-open-throttle accelerations, decelerations, and short-term cruise and idle conditions typical of urban traffic. The varying modes result in the discharge of much larger particles. Robinson and Ludwig[11] reported MMED of 0.25 µm for urban and rural areas; 25 percent of the particles were smaller than 0.16 µm, and 25 percent were larger than 0.43 µm (Table 6-1). Cholak et al.,[12] Lee et al.,[13] and Flesch[14] observed similar distributions; however, their data also indicate that these distributions change very little over distances.

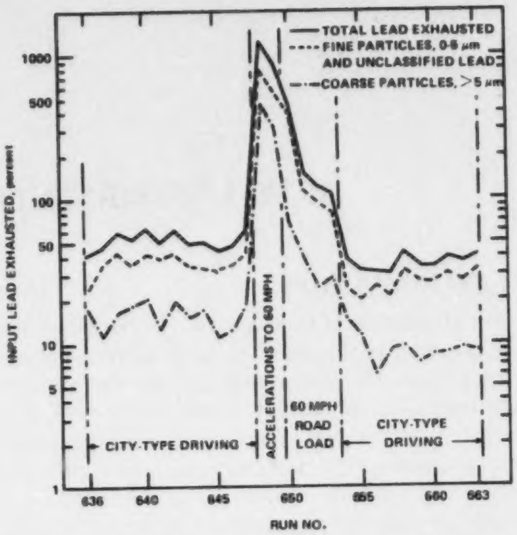

Figure 6-2. Effect of various driving conditions on the amount of lead exhausted.[4]

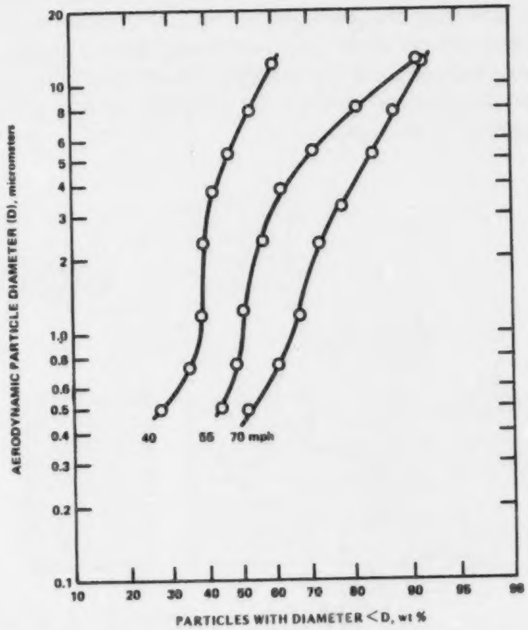

Figure 6-3. Effect of speed on size distribution of exhaust particles at different road load cruise conditions and using Indolene HO 0 fuel.[3]

Gillette and Winchester[15] examined the effect of age on the size distribution of lead aerosols. They found that lead aerosol size distributions do not vary greatly from one source area (essentially an area of heavy automobile traffic) to another, and that the

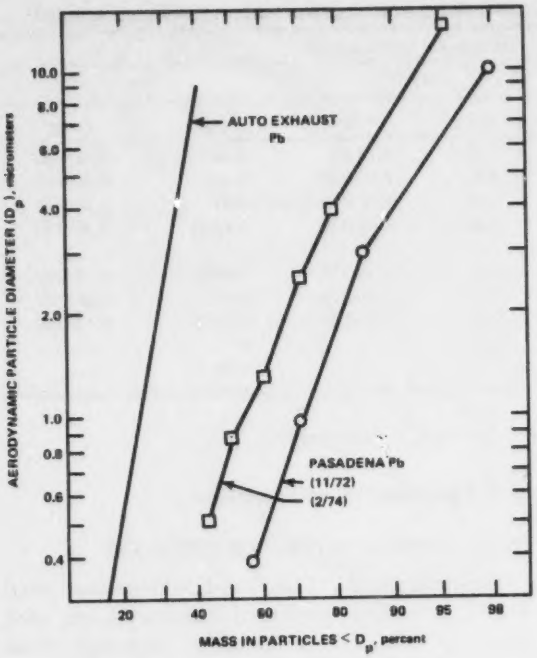

Figure 6-4. Cumulative mass distributions for lead aerosol in auto exhaust and at Pasadena, a receptor sampling site. The abscissa is a log-normal scale, and D_p is the aerodynamic, unit density particle diameter.[10]

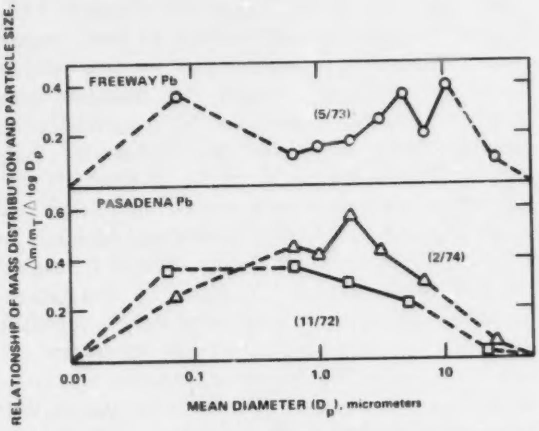

Figure 6-5. Differential mass distributions for lead 1 m from a freeway, May 1973, and at Pasadena sampling sites, November 1972 and February 1974. (The abscissa is the mean diameter, and the dashed lines assume that the smallest particle size is 0.01 μm and the largest 50 μm. $\Delta \log D_p$ = interval of log of aerodynamic particle diameter; m_T = total mass loading of lead in airborne particulates; Δm = mass of lead occurring in a fraction, defined in terms of size, of the total particulates; $\Delta m/m_T$ = fraction of mass occurring in a given particle size range.)[10]

lead aerosol size distributions do not respond noticeably to changes in weather within a source area during 24-hr sampling periods. The results of their study suggest little modification of the characteristics of the lead aerosol size distribution as a result of nonprecipitative atmospheric mechanisms for equivalent particle radii larger than 0.2 μm.

Electron microscope studies have shown that many of the fine particles in exhaust emissions are nearly spherical in shape and are electron-dense. The coarser particles are much more irregular, and some are filamentous in outline. Particles collected at a constant cruise speed of 30 mph were found to be composed of a carbon core or matrix, on or in which were distributed spherical or crystalline electron-dense lead particles <0.1 μm in diameter.[3,16] Electron micrographs of the exhaust particles have shown that although the particle aggregates of about 0.5 μm were stable, samples of the gas that had been inhaled showed more homogeneous aggregates 1 to 2 micrometers in diameter than larger aggregates in the exhaled gas. A similar effect was obtained by drawing the gas through a humidifier.[17]

6.2.1.2 SIZE DISTRIBUTION OF PARTICLES FROM STATIONARY SOURCES

High-temperature combustion and smelting processes generate submicrometer-sized lead particulate, whereas lead emissions from material handling and mechanical attrition operations associated with smelters consist of larger (> 1 μm) dust particles. Actual data on the size distribution of lead particles emitted from stationary sources are limited. Fugas et al.,[18] using a five-stage impactor, obtained samples in the Meza Valley (influenced by a lead smelter) and in the urban area of Zagreb. The results are shown in Figure 6-6. A considerable difference was found in the size distribution of lead particles in the industrial (Meza Valley) versus the urban (Zagreb) area. In the industrial area, only 10 percent of the lead particles had diameters smaller and 1 μm, whereas in the urban area, 75 percent were smaller than 1 μm. This implies that the fugitive dust from the mechanical rather than the direct-smelting operation is the primary emission.

Lead emissions from stationary sources are probably affected by topographic influences in a manner similar to other pollutants. Because of the mountainous location of half of the six primary lead smelters in the United States, however, and because these three smelters are probably the largest single-point emitters of lead, the topographic influence on transport and dispersion is important.

TABLE 6-1. COMPARISON OF SIZE DISTRIBUTIONS OF LEAD-CONTAINING PARTICLES IN MAJOR SAMPLING AREAS[11]

		Distribution by particle size, μm					
		25%		MMED[a]		75%	
Sample area	No. of samples	Avg.	Range	Avg.	Range	Avg.	Range
Chicago	12	0.19(7)[b]	0.10-0.29	0.30	0.16-.64	0.40(10)	0.28-0.63
Cincinnati	7	0.15(3)	0.09-0.24	0.23	0.16-0.28	0.44	0.30-0.68
Philadelphia	7	0.14(3)	0.09-0.25	0.24	0.19-0.31	0.41	0.28-0.56
Los Angeles (DTN)	8	0.16(7)	0.10-0.22	0.26	0.19-0.29	0.49(7)	0.39-0.60
Pasadena	7	0.18	0.05-0.25	0.24	0.08-0.32	0.48(6)	0.13-0.67
Vernon (rural)	5	0.17(4)	0.12-0.22	0.24	0.18-0.32	0.40	0.28-0.47
San Francisco	3	0.11	0.06-0.13	0.25	0.15-0.31	0.45(2)	0.44-0.46
Cherokee (rural)	1	0.25	—	0.31	—	0.71	—
Mojave (rural)	1	—	—	0.27	—	0.34	—

[a] MMED = mass median equivalent diameter.

[b] Numbers in parentheses indicate number of samples available for a specific value when different from total number of samples.

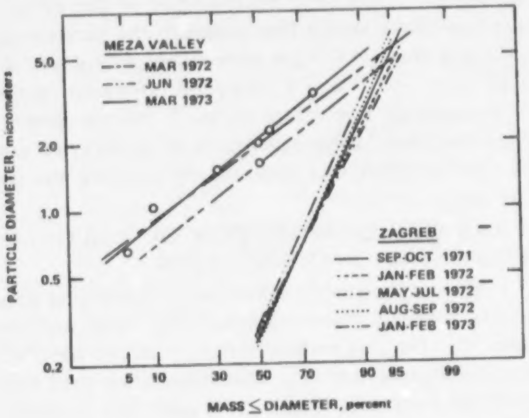

Figure 6-6. Cumulative mass distribution of lead particles by size.[18]

At least four general conclusions about lead from mobile and stationary sources can be based on the results of the above studies:

1. Lead is emitted into the atmosphere principally in the particulate form.
2. The mass median equivalent diameters of the lead-bearing particles are typically less than 1 μm, and the size distributions are fairly uniform from area to area.
3. The particle sizes in urban and rural areas are such that the lead can be transported over relatively large distances via typical atmospheric convection and turbulence processes.
4. The size distributions are such that significant fractions of the total atmospheric lead concentrations are within the respirable size range.

6.2.2 **Chemical Transformations**

6.2.2.1 MOBILE SOURCE EMISSIONS

Tetraethyl lead (TEL) and tetramethyl lead (TML), as well as the mixed-lead alkyls, are used widely as additives in gasoline. Although these organic compounds are less volatile than gasoline, small amounts may escape to the atmosphere by evaporation from fuel systems or storage facilities. TEL and TML are light-sensitive and undergo photochemical decomposition when they reach the atmosphere.[10,19] The lifetime of TML appears to be longer than that of TEL. Exposure of dust to TEL, both in the presence and absence of water vapor, results in sorption of organic lead on dust particle surfaces.[20] Laveskog[21] found that transient peak lead alkyl concentrations up to 5000 μg lead/m³ in exhaust gas may be reached in a cold-started, fully choked, and poorly tuned vehicle. If a vehicle with such emissions were to pass a sampling station on a street where the lead alkyl level might typically be 0.02 to 0.04 μg/m³ of air, a peak of about 0.5 μg/m³ could be measured as the car passed by. The data reported by Laveskog were obtained with a procedure that collected very small (100 ml), short-time (10 min) air samples. The sensitivity reported was much better than that reported by other investigators, who have not been able to duplicate his results.[22] Harrison et al.[22] found levels as high as 0.59 μg/m³ (9.7 percent of total lead) at a busy gasoline service station.

Purdue et al.[23] measured particulate and organic lead in atmospheric samples. Some results are shown in Tables 6-2 through 6-4. These data demonstrate that in all of the cities studied, particulate lead levels are much higher (an average of approximately 20 times higher) than organic lead levels. The results are entirely consistent with the studies of Huntzicker et al.,[10] who report an organic component of 6 percent of the total airborne lead in Pasadena for a 3-day period in June 1974, and of Skogerboe,[24] who measured fractions in the range of 4 to 12 percent at a site in Fort Collins, Colorado. It is noteworthy, however, that in the underground garage (Table 6-4), total lead concentrations are approximately five times those in the urban areas, and the percentage of organic lead increases to approximately 17 percent. Consequently, the concentration of organic lead in an underground garage site is ten times that in the open urban environment (see Tables 6-2 and 6-4), and the potential exposure level is similarly magnified.

TABLE 6-2. RESULTS OF ATMOSPHERIC SAMPLING FOR ORGANIC AND PARTICULATE LEAD[23] ($\mu g/m^3$)

Sample no.[a]	Cincinnati		Denver		Washington, D.C.		St. Louis		Philadelphia		Chicago	
	Organic[b]	Particulate[c]	Organic	Particulate	Organic	Particulate	Organic	Particulate	Organic	Particulate	Organic	Particulate
1	0.2	1.5	0.2	2.3	0.0	1.4	0.5	2.0	0.5	1.3	0.2	5.9
2	0.0	0.9	0.5[d]	1.8	0.2	1.4	0.2	2.0	1.1[d]	1.7	0.4	5.6
3	0.0	0.9	1.4[d]	1.6	0.1	1.5	0.4	1.8	0.2	2.9	0.2	5.3
4	0.2	1.9	0.3	1.7	0.3	1.0	0.2	2.5	0.4	2.4	1.6[d]	3.5
5	0.4	3.7	0.2	1.0	0.1	1.1	0.3	1.9	0.8	1.1	0.2	4.6
6	0.2	1.6	0.1	1.8	0.1	0.8	0.2	1.8	0.4	1.1	0.2	5.5
7	0.2	1.8	0.0	2.2	0.1	1.7	0.3	2.2	0.0	1.7	0.3	5.8
8	0.4	1.3	0.2	1.8	0.2	1.2	0.4	2.2	0.3	2.1	0.1	4.8
9	0.2	1.5	0.2	2.0	0.4	0.8	0.4	2.0	0.1	1.8	0.2	5.0
10	0.2	2.4	0.5[d]	—	0.2	1.6	1.3[d]	1.2	0.1	2.3	0.2	5.1
Avg.	0.2	1.7	0.2	1.8	0.2	1.2	0.3	2.0	0.3	1.8	0.2	5.1

[a] Sample no. represents order in which samples were taken. Cities were not sampled concurrently.
[b] All values are average of two determinations.
[c] Determined by NASN method (6).
[d] Organic lead averages do not include these values because the replicate values for these samples were more than twice the standard deviation from the average.

TABLE 6-3. PERCENTAGE OF PARTICULATE VERSUS VAPOR-PHASE LEAD IN URBAN AIR SAMPLES[23]

City	Total lead[a]		Particulate, % of total
	Organic, $\mu g/m^3$	Particulate, $\mu g/m^3$	
Cincinnati	0.2	1.7	89
Denver	0.2	1.8	90
Washington, D.C.	0.2	1.2	86
St. Louis	0.3	2.0	87
Philadelphia	0.3	1.8	86
Chicago	0.2	5.1	96

[a] All values are averages of ten determinations.

[b] Percent particulate Pb = $\frac{\text{particulate Pb} \times 100}{\text{organic Pb} + \text{particulate Pb}}$

TABLE 6-4. ANALYSES OF FIVE REPLICATE SAMPLES TAKEN IN AN UNDERGROUND PARKING GARAGE[23]

Sample no.	Organic lead, $\mu g/m^3$	Organic lead, %	Particulate lead, $\mu g/m^3$	Total lead, $\mu g/m^3$
1	1.9	15.7	10.3	12.2
2	1.9	17.1	9.2	11.1
3	1.9	17.6	8.9	10.8
4	1.8	14.9	10.3	12.1
5	2.2	18.0	10.0	12.2
Average ($\bar{X}$)	1.9	16.7	9.7	11.6
Relative standard deviation (Srel)[a]	7.9%	7.9%	6.7%	5.2%

[a] Srel = $\frac{\text{Standard deviation}}{\text{Average}} \times 100$

As the lead alkyl compounds of gasoline are subjected to the elevated temperatures and pressure of combustion, they are converted to lead oxides, which function to inhibit engine knock. The lead oxides react with other additives in the fuel and leave the combustion chambers in a variety of complex compounds. The results of composition studies by Hirschler and Gilbert,[4] Ter Haar et al.,[2] and Ter Haar and Bayard[25] are shown in Tables 6-5 and 6-6, respectively.

Habibi et al.[5] determined the composition of particulate matter emitted from a test car operating on a typical driving cycle. The main conclusions drawn from the study were:

1. Composition of emitted exhaust particles is related to particle size.
2. Very large particles greater than 200 μm have a composition similar to lead-containing material deposited in the exhaust system, confirming that they have been re-entrained or have flaked off from the exhaust system. These particles contain approximately 60 to 65 percent lead salts, 30 to 35 percent ferric oxide (Fe_2O_3), and 2 to 3 percent soot and carbonaceous material. The major lead salt is lead bromochloride (PbBrCl), with large amounts (15 to 17 percent) of lead oxide

TABLE 6-5. AVERAGE COMPOSITION OF PARTICULATE LEAD COMPOUNDS EMITTED IN AUTO EXHAUST[a,2,4]

Exhaust source	Compound,[b] wt. %				
	PbCl·Br	αNH$_4$Cl·2PbCl·Br	βNH$_4$Cl·2PbCl·Br	2NH$_4$Cl·PbCl·Br	3Pb$_3$(PO$_4$)$_2$ PbCl·Br
Car B:					
City type cycle, fuel plus TEL motor mix only	68	24	6	2	—
City type cycle, added sulfur[c]	70	30	—	—	—
City type cycle, added phosphorus[d]	35	18	17	10	20
Constant speed, 60 mph, road load	60	20	20	—	—
Full-throttle accelerations	85	10	5	—	—
Car M:					
City type cycle, fuel plus TEL motor mix only	33	40	5	22	—
Constant speed, 60 mph, road load	30	30	35	5	—
Full-throttle accelerations	90	10	—	—	—

[a] X-ray diffraction analyses made *in situ* on material deposited on glass slides mounted within the precipitator of the sampler.

[b] In addition to the tabulated compounds, PbSO$_4$ and PbO·PbCl·Br·H$_2$O occurred ocasionally in concentrations of 5 percent or less.

[c] Sulfur content increased from 0.025 to 0.105 weight percent by addition of disulfide oil.

[d] 0.4 theory phosphorus added.

TABLE 6-6. EFFECTS OF AGING ON LEAD COMPOUNDS IN SAMPLES OF AUTO EXHAUST AS DETERMINED BY ELECTRON MICROPROBE[25]

Lead compound	Percentage of total particles sampled				
	Black bag[a]		Eight-Mile Road[b]		Rural site[c]
	Zero time	18 hour	Near road	400 yd	
PbCl$_2$	10.4	8.3	11.2	10.5	5.4
PbBr$_2$	5.5	0.5	4.0	0.7	0.1
PbBrCl	32.0	12.0	4.4	0.6	1.6
Pb(OH)Cl	7.7	7.2	4.0	8.8	4.0
Pb(OH)Br	2.2	0.1	2.0	1.1	—
(PbO)$_2$·PbCl$_2$	5.2	5.6	2.8	5.6	1.5
(PbO)$_2$·PbBr$_2$	1.1	0.1	0.7	0.3	—
(PbO)$_2$·PbBrCl	31.4	1.6	2.0	0.6	1.0
PbCO$_3$	1.2	13.8	15.6	14.6	30.2
Pb$_3$(PO$_4$)$_2$	—	—	0.2	0.3	—
PbO$_x$	2.2	21.2	12.0	25.0	20.5
(PbO)$_2$·PbCO$_3$	1.0	29.6	37.9	21.3	27.5
PbO·PbSO$_4$	—	0.1	1.0	4.6	5.0
PbSO$_4$	0.1	—	2.2	6.0	3.2

[a] Sample collected directly from tailpipe in black bag to prevent irradiation of exhaust. Analyzed immediately and again 18 hr later to determine effect of aging.

[b] State highway in Detroit carrying about 100,000 cars a day.

[c] Samples were taken 400 yd from a lightly traveled roadway.

(PbO) occurring as the 2 PbO·PbBrCl double salt. Lead sulfate and lead phosphate account for 5 to 6 percent of these deposits. (These compositions resulted from the combustion of low-sulfur and low-phosphorus fuel.)

3. PbBrCl is the major lead salt in particles of 2 to 10 micrometers equivalent diameter, with 2 PbBrCl·NH$_4$Cl present as a minor constituent.
4. Submicrometer-sized lead salts are primarily 2PbBrCl·NH$_4$Cl.
5. Lead-halogen molar ratios in particles of less than 10 microns MMED indicate that much more halogen is associated with these solids than the amount expected from the presence of 2PbBrCl·NH$_4$Cl, as identified by X-ray diffraction. This is particularly true for particles in the 2- to 0.5-micrometer size range.
6. There is considerably more soot and carbonaceous material associated with small particles than with coarse particles reentrained after having been deposited after emission from the exhaust system. This carbonaceous material accounts for 15 to 20 percent of the finer particles.
7. Particulate matter emitted under typical driving conditions is rich in carbonaceous-type material. There is substantially less such material emitted under continuous hot operation.
8. Only small quantities of 2PbBrCl·NH$_4$Cl were found in samples collected at the tail-

pipe from the hot exhaust gas. Its formation therefore takes place primarily during cooling and mixing of exhaust with ambient air.

Hirschler and Gilbert[4] found similar results and speculated that higher gas temperature during full-throttle operations reduced the tendency for the ammonium-lead halide complexes to be present since they are unstable at high temperatures.

Based on the above studies, it seems quite clear that the size distribution of lead particles emitted from automobiles and the relative concentrations of the complex compounds in those particles vary significantly with driving conditions, engine condition, type of fuel, and age of exhaust system. Particles > 2 μm in the exhausted particulate are primarily lead bromochloride. The very large particles, a consequence of deposits in the exhaust system, are also primarily lead bromochloride.

The fates of these lead compounds, once they are introduced into the atmosphere from automobiles, are not completely understood. There is disagreement in the early literature concerning the loss of halogens by these lead compounds. Pierrard[26] suggested that PbBrCl undergoes photochemical decomposition with the formation of a lead oxide and the release of free bromine and chlorine, but later suggested a hydrolytic conversion mechanism. Ter Haar and Bayard[25] and Robbins and Snitz[27] confirm the loss of halogen from freshly emitted Pb salts, but they do not support the photochemical mechanism. Ter Haar and Bayard[25] suggest that lead halides are eventually converted to lead carbonates and lead oxides. Pierrard[26] obtained data on aged lead aerosol that indicated that the lead particle surfaces had already been converted to a relatively insoluble form such as oxide, carbonate, or basic halide; this would be consistent with a conversion mechanism expected to release the less reactive hydrogen halide rather than the more reactive molecular halogen. Dzubay and Stevens[28] observed a diurnal variaton in the bromine-to-lead concentration ratio in atmospheric particulate indicative of the loss of halogens during atmospheric transport. Ter Haar and Bayard[25] studied the effects of aging on automobile exhaust collected in a black bag, using an electron probe. The results, shown in Table 6-6, indicate that 75 percent of the bromine and 30 to 40 percent of the chlorine associated with the compounds contained in the particulates were lost in 18 hr; data presented suggest that the proportions of lead carbonates and lead oxides increased. Since these chemical reactions occurred in a black bag, photolytic processes would not likely be responsible for the decrease in halides. At the very least, therefore, this experiment demonstrates the existence of nonphotolytic decomposition pathways for lead halides in the atmosphere. Consequently, the chemical composition of lead in the atmosphere from automobile emissions almost certainly depends to some extent on the age of the particles as well as the presence of other pollutants with which the lead compounds can react.

The results of Lee et al.[9] show that the percentage of water-soluble particulate lead increased when diluted exhaust was irradiated by light in the wavelength region of 3000 to 6000 Å. This region is in the near-ultraviolet and visible regions of the spectrum and is available from direct sunlight. The percentage of water-soluble lead in the diluted exhaust also was increased by irradiation in the presence of 0.5 ppm SO_2. Irradiation significantly increased the sulfate concentration of the particulates and was accompanied by a shift to smaller particle sizes. A shift of nitrate-bearing particles to smaller sizes, with and without addition of SO_2, was also observed with irradiation. The amount of nitrate present was decreased in the presence of SO_2. The lead nitrate, which is much more soluble in water than the other lead salts present, cannot be totally responsible for the increased water solubility observed if the NO_3 concentrations decrease.

The information available regarding the chemical composition of lead particles emitted from automobiles may be summarized as follows:

1. Lead halogen compounds are the principal forms emitted; lead chlorobromide is the most prominent of these.
2. The particulates undergo compositional changes during transport away from the source. These changes appear to consistently involve:
   a. Losses of halogens, the rate of which might be photochemically enhanced, but which also occur in the absence of light.
   b. General increases in the water solubilities of the particles with concomitant shifts toward smaller mean particle sizes. These latter changes are enhanced by the presence of SO_2, in which case the amounts of nitrate present decrease.
3. Although several reports have suggested that the lead halogen compounds are converted to oxides and/or carbonates, the only specific examination of the composition after aging was that of Ter Haar and Bayard.[25] Unfortunately, their experimental approach did

not rely on a particularly definitive method of identification. Indeed, the electron microprobe approach used can only be regarded as a crude qualitative tool for the identification of compounds; the simultaneous occurrences of other elements in lead-bearing particles and the general morphological characteristics of the particles can provide only circumstantial indications of the compounds that are present. This is particularly true for lead-bearing particles because compounds of several other elements are also typically present. Habibi et al.,[5] for example, have shown that the particles often include iron as well as lead compounds. The percentage composition data given in Table 6-6 should also be evaluated, taking into account that they are number rather than mass percentages. Thus, although lead carbonate, for example, may comprise a relatively high number percentage of the total, its mass percentage may be quite different, depending on the size distributions involved and whether the particle compositions are size dependent.

These general conclusions and qualifications are consistent with and supportive of the results of the study reported by Olson and Skogerboe.[29] They determined that the principal form of lead found in lead-contaminated soils from highway medians as well as in street dusts was lead sulfate. Although this study included evaluation of 18 soil and/or dust samples collected from different U.S. locations, significant amounts of the lead halogen compounds were found in any case. The conversion of lead halides to other compounds appears to have been quite complete for these aged lead aerosol deposits.

6.2.2.2 STATIONARY SOURCE EMISSIONS

Measurements are not available to confirm the chemical form of lead emissions from stationary sources. Barltrop and Meek[30] indicate the presence, without reference to specific measurements, of lead sulfide or lead chloride in the mining industry, lead oxide in smelters, and lead carbonate and lead chromate in pigments used in older paints. Lead oxide is the principal form of the metal used in battery manufacturing.

The association of lead sulfide with mining is clearly rational, since this is the primary mineral form (galena). While lead oxide may certainly be derived from the smelting process, the amounts produced may be relatively small in comparison to the amounts of lead sulfide released as fugitive dust to the atmosphere around a smelter. Moreover, the release of SO_2 usually associated with lead smelting operations, coupled with the possible interactions between lead particles and SO_2, imply that the compounds released may well undergo conversion to other forms. Thus, although the compounds generally associated with stationary sources are not particularly soluble, the possibility of conversion to more soluble compounds or accumulation of the particles in the lungs of exposed populations should not be ignored.

6.3 TRANSPORT IN AIR

The mechanisms of atmospheric transport, removal, and resuspension of lead particulates interact in a complex manner. The transport mechanisms are functions of the particle size distribution, particle morphology, meteorology, and local topography.

6.3.1 Distribution Mechanisms

The transport and diffusion of gaseous and particulate materials in the atmosphere are consequences of molecular diffusion and the three-dimensional motion field, the latter being the dominant factor. A detailed treatment of these phenomena will be found in many standard textbooks on meteorology. The three-dimensional motion field can be assumed to be composed of a mean wind (transport) vector and a turbulent component. The turbulent component is analogous to molecular diffusion, but the coefficient of turbulent eddy diffusion is usually of much greater magnitude. The turbulent component tends to spread the material vertically and laterally about the mean horizontal transport vector. Therefore, assuming a pollution plume from a local line or point source, the atmospheric motion serves to dilute and transport the pollutants.

Since lead emitted to the atmosphere is primarily in the inorganic particulate form, its transport and dispersion will depend primarily on particle size as well as chemical stability, the height of injection, and the intensity and stability of the atmospheric motion field. Large particles injected at low elevations will settle to the surface in the immediate vicinity of the source, whereas the smaller particles will be transported over greater distances.

A study by Daines et al.[31] related atmospheric lead to traffic volume and distance from a highway. They found the effect of traffic on lead content of the air to be striking, but limited to a rather narrow zone bordering primarily the lee side of the highway, as shown in Figure 6-7. About 65 percent of the lead in the air between 30 and 1750 ft from the highway consisted of particles under 2 μm, and 85 percent were under 4 μm in diameter. Figure 6-8 shows a typical relationship of particle size to distance from the highway. Cholak et al.[12] and Schuck and Locke[32] did similar studies with similar results. As shown in Figures 6-4 and 6-5, Huntzicker et al.[10] demonstrated that the large particle mode ($D_p > 7\ \mu m$) in the freeway distribution is severly attenuated at the Pasadena site.

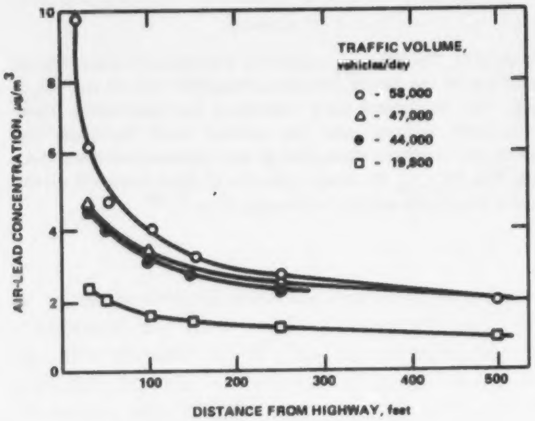

Figure 6-7. Air-lead values as a function of traffic volume and distance from the highway.[31]

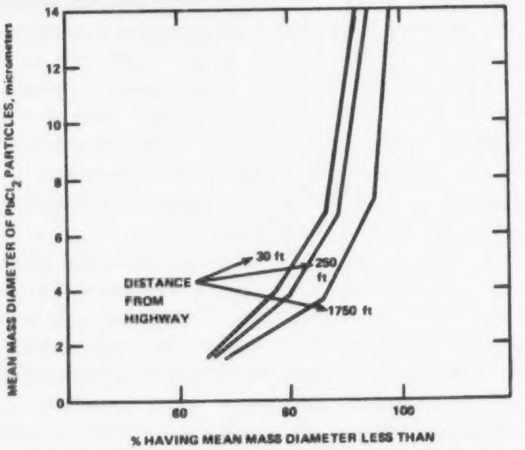

Figure 6-8. Relationship of the diameter of the particles (mass) to distance from the highway.[31]

Knowledge of lead concentrations in the oceans and glaciers provides some insight into the degrees of atmospheric mixing and long-range transport. Tatsumato, Patterson, and Chow[33-35] measured dissolved lead concentrations in sea water off the coast of California, in the Central North Atlantic (near Bermuda), and in the Mediterranean. The profiles obtained are shown in Figure 6-9. Surface concentrations in the Pacific were found to be higher than those of the Mediterranean or the Atlantic, and decreased abruptly to relatively constant levels with depth. The vertical gradient was found to be much less in the Atlantic. Based on the Pacific data, Tatsumato and Patterson[33] estimated an average surface lead concentration of 0.2 μg/kg in the northern hemispheric oceans. Chow and Patterson[35] revised this estimate downward to 0.07 μg/kg. There appears to be no difference between lead concentrations in deep water in the Atlantic and Pacific. These investigators calculated that industrial lead is currently being added to the oceans at about 10 times the rate of introduction by natural weathering, with significant amounts being removed from the atmosphere by precipitation and deposited directly into the ocean. Their data suggest considerable contamination of surface waters near shore, diminishing toward the open ocean.[35] These investigators conclude that lead emissions from automobiles are the primary source of pollution of ocean surface water.

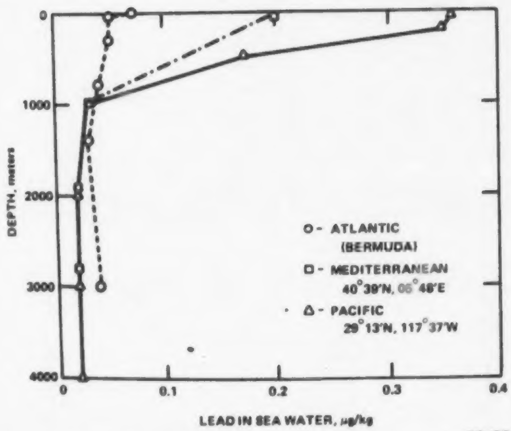

Figure 6-9. Lead concentration profiles in the oceans.[33-35]

Duce, Taylor, Zoller, and their co-workers[36-38] have investigated trace-metal concentrations (including lead) in the atmosphere in remote northern and southern hemispheric sites. The natural sources for such atmospheric trace metals include the oceans and the weathering of the earth's crust, whereas the manmade source is particulate pollution. Enrichment factors for concentrations relative to standard values for the oceans and the crust were calculated (Table 6-7); the mean crustal enrichment factors for the North Atlantic and the South Pole are shown in Figures 6-10 and 6-11. The significance of the comparison in Figure 6-11 is that 90 percent of the particulate pollutants in the global troposphere are injected in the northern hemisphere.[39] Since the residence times for particles in the troposphere[40] are much less than the interhemispheric mixing time, it is unlikely that significant amounts of particulate pollutants can migrate from the North Atlantic to Antarctica via the troposphere; however this does not rule out stratospheric transfer. In the case of lead (and all other metals studied except vanadium), the enrichment factors were very similar at the two locations. This suggests (but does not prove) that the atmospheric concentrations of these metals may originate primarily from natural (rather than man-made) sources.

TABLE 6-7. CONCENTRATION RANGE AND MEAN EF_{crust} VALUES FOR ATMOSPHERIC TRACE METALS COLLECTED OVER THE ATLANTIC NORTH OF 30° N[36]

Element	Concentration range, ng/scm	EF_{crust}, geom. mean[a]
Al	8-370	1.0
Se	0.0008-0.011	0.8
Fe	3.4-220	1.4
Co	0.006-0.09	2.4
Mn	0.05-5.4	2.6
Cr	0.07-1.1	11
V	0.06-14	17
Zn	0.3-27	110
Cu	0.12-10	120
Cd	0.003-0.62	730
Pb	0.10-64	2,200
Sb	0.05-0.64	2,300
Se	0.09-0.40	10,000

[a] Calculated on the basis of the mean crustal abundances of Taylor.[37]

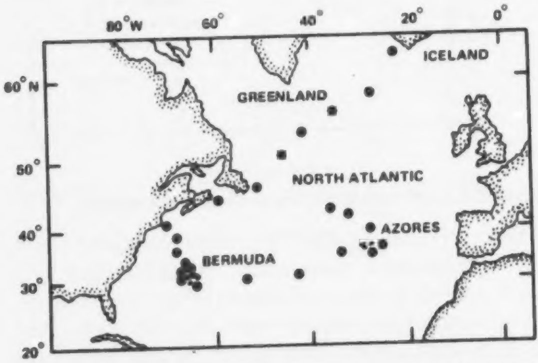

Figure 6-10. Midpoint collection location for atmospheric samples collected from R. V. *Trident* north of 30°N, 1970 through 1972.[36,38]

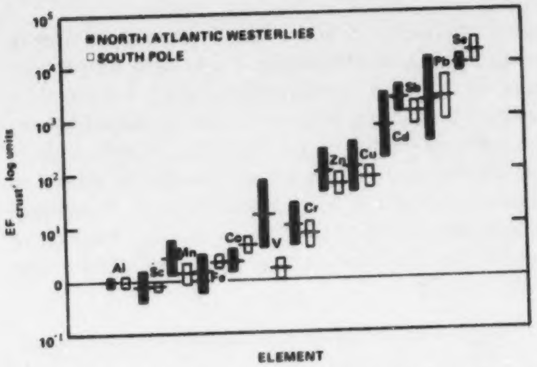

Figure 6-11. The EF_{crust} values for atmospheric trace metals collected in the North Atlantic westerlies and at the South Pole. The horizontal bars represent the geometric mean enrichment factors, and the vertical bars represent the geometric standard deviation of the mean enrichment factors. The EF_{crust} for lead at the South Pole is based on the lowest lead concentration (0.2 mg/scm).[36,38]

Murozumi et al.[41] have presented supportive evidence. Their data show that long-range transport of lead aerosols emitted from automobiles has significantly polluted the polar glaciers. They collected samples of snow and ice from Greenland and the Antarctic. As shown in Figure 6-12, they found that the concentration of lead varied inversely with the geological age of the sample. The authors attribute the gradient increase after 1750 to the Industrial Revolution and the enhanced increase after 1940 to the increased use of lead alkyls in gasoline. The most recent levels fround in the antarctic snows were, however, less than those found in Greenland by a factor of 10 or more. Before 1940, the concentrations in the Antarctic were below the detectable level (< 0.001 μg/kg) and have risen to 0.2 μg/kg in recent snow. A graph of the world lead smelter and lead alkyl production presented by Murozumi et al.[41] is shown in Figure 6-13; supporting data are shown in Table 6-8.

The results and conclusions of Murozumi et al. were criticized by Mills,[42] who suggested the increase in the snow lead after 1940 could be due to aircraft operating from Thule Air Force Base. Bryce-Smith[43] countered Mills' argument by stating that the greatest amount of lead found to be deposited in the snow was during winter months when air traffic was lightest; there was no horizontal gradient between the air base and the collecting site; the collecting site was predominantly upwind from the air base; and, finally, the major increase in lead levels began about 20 years before the nearest operating base was established.

Jaworowski[44] found that lead concentrations in two glaciers have increased by a factor of 10 during the last century. The concentrations in the most re-

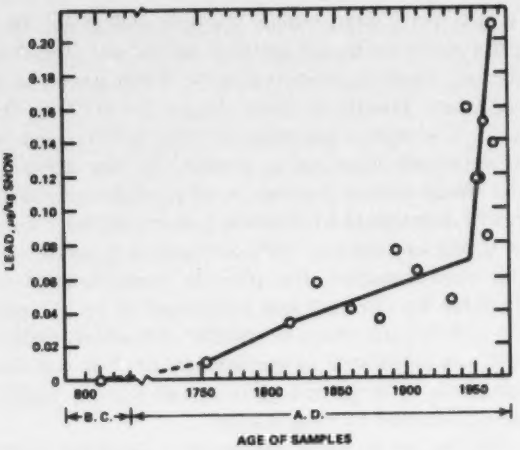

Figure 6-12. Lead concentration profile in snow strata of Northern Greenland.[41]

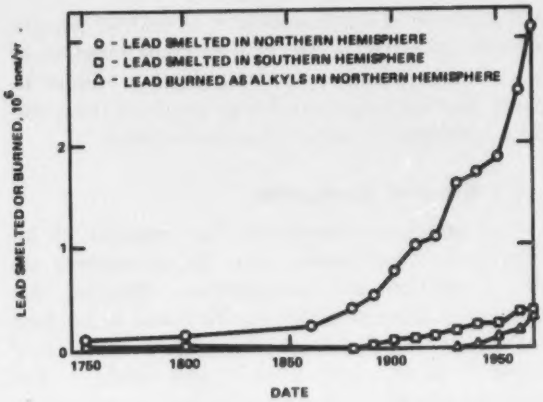

Figure 6-13. World lead smelter and alkyl lead production since 1750 A.D.[41]

TABLE 6-8. LEAD AEROSOL PRODUCTION IN THE NORTHERN HEMISPHERE COMPARED WITH LEAD CONCENTRATIONS IN CAMP CENTURY, GREENLAND, SNOW AT DIFFERENT TIMES[41]

Date	Lead smelted, 10^3 tons/yr	Fraction converted to aerosols, %	Lead aerosols produced from smelteries, 10^3 tons/yr	Lead burned as alkyls, 10^3 tons/yr	Fraction converted to aerosols, %	Lead aerosols produced from alkyls, 10^3 tons/yr	Total lead aerosols produced, 10^3 tons/yr	Lead concentration at Camp Century, µg/kg snow
1753	1	2	2	—	—	—	2	0.01
1815	2	2	4	—	—	—	4	0.03
1933	16	16	8	0-1	40	4	12[a]	0.07
1966	31	0.06	2	3	40	100	102[a]	0.2

[a] Values corrected.

cent ice layers were extremely high (148 µg/kg). Jaworowski et al.[45] also studied stable and radioactive pollutants from ice samples from Storbreen glaciers in Norway. The mean stable lead concentration in Storbreen glacier ice in the 12th century was 2.13 µg/kg. The mean for more recent samples was 9.88 µg/kg. Around 1870, the average lead concentration in Norwegian glacier ice was 5.86 µg/kg, whereas that for glaciers in Poland was 5.0 µg/kg. A century later, the mean concentration in the Norwegian glacier was 9.88 µg/kg, whereas the mean concentration in the Polish glacier reached 148 µg/kg. Jaworowski et al.[45] attributed the large increase of lead concentrations in the Polish glacier to local sources.

Jaworowski et al.[45] also measured ^{210}Pb in the glacier ice. The values found in the Storbreen glacier ice are shown graphically in Figure 6-14. The highest value was found in 1961. A similar value was found in Polish glaciers and in the Alps the same year.[44] The values and irregularities observed in ^{210}Pb concentrations in the investigations suggest that part of the atmospheric ^{210}Pb may have originated from artificial sources — nuclear explosions in the Arctic, or energy production in fossil-fuel power stations. Based on their findings, Jaworowski et al.[45] concluded that long-range transport of lead

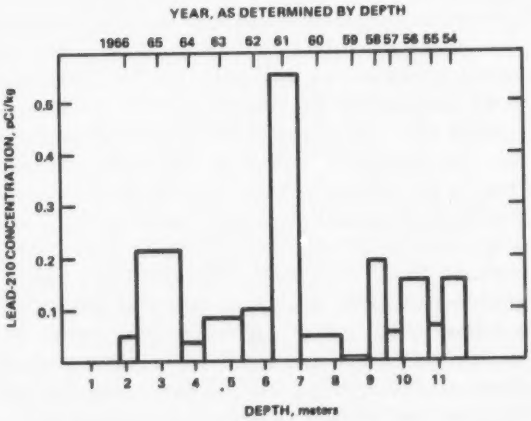

Figure 6-14. ^{210}Pb in Storbreen, Norway, glacier ice, 1954-1966.[45]

pollutants in the atmosphere is a reality, but the authors suggest that the rate of contamination of glacier ice correlates better with the total annual input of coal burning to the energy system of the world than with lead emissions from automobiles.

6.3.2 **Removal Mechanisms**

The principal mechanisms for removal of inorganic lead particulate from the atmosphere are dry deposition and precipitation. Detailed discussions of these processes will be found in standard textbooks by Sutton,[46] Pasquill,[47] Fletcher,[48] Junge,[49] Green and Lane,[50] and Slade.[51] The removal efficiency of these processes varies significantly, depending on physical characteristics of the suspended material, atmospheric conditions, and the nature of the receiving surface.

6.3.2.1 DRY DEPOSITION

Dry deposition removal processes include sedimentation, diffusion, and inertial mechanisms such as impaction. Sedimentation, or settling of particles, occurs when the mass of the particle is large enough to overcome the buoyancy force and the lifting forces of convective currents. Freely falling particles of the size range found in suspended aerosols rapidly attain their terminal, or constant, velocity when the aerodynamic drag on the particle is equal to the weight of the particle. The terminal velocity depends on the particle size, its density, and gravitational acceleration. When a particle is of a size comparable to the mean free path of the gas molecules, bombardment by the molecules results in a random or Brownian motion that is superimposed on its downward motion. If a particle is very small and its motion is observed for only a short period of time, its fall may be completely masked by the Brownian motion. Residence times or, conversely, the rate of fallout of aerosols or dust particles containing lead in the atmosphere are then primarily a function of particle size. The shape of the suspended particles also has a significant effect on the settling velocity. Usually the settling velocity of particles of various geometrical forms is calculated in terms of the settling velocity of spherical particles of the same volume. The aerodynamic particle size, conventionally used when discussing airborne particulate, is defined as the size of a sphere of unit density that has identical aerodynamic behavior to the particle in question. Particles having the same aerodynamic size may have differing shapes and dimensions.

Airborne particles are generally divided into three size ranges: Aitken nuclei (particle radius < 0.1 μm), large nuclei (particle radius 0.1 to 1 μm), and giant nuclei (particle radius > 1 μm). Extremely small particles (radius < 0.001 μm) tend to coagulate rapidly to form larger (~ 0.05 to 0.5 μm), less mobile particles.[50] Fletcher[48] derived an approximate equation to predict the rate at which the concentration number, n, of particles of radius, r, will decrease in a relatively uniform aerosol. For $r = 0.005$ μm and $n = 10^5/cm^3$ (typical in urban air), the time required for particle concentration to decrease by one-half was calculated to be 30 min. For $r = 0.1$ μm and $n = 10^3/cm^3$, 50 percent reduction was calculated to require 500 hr. The size distributions of large and giant nuclei are not significantly affected by coagulation.

Settling or terminal velocities of spherical particles, as reported by Green and Lane[50] and Israel and Israel,[52] are shown in Table 6-9.

TABLE 6-9. TERMINAL VELOCITIES OF SPHERICAL PARTICLES OF UNIT DENSITY AT GROUND LEVEL

Particle radius, μm	Terminal velocity, cm/sec	
	Israel and Israel[52]	Green and Lane[50]
0.01	1.43×10^{-5}	—
0.05	—	8.71×10^{-5}
0.1	2.32×10^{-4}	2.27×10^{-4}
0.2	—	6.85×10^{-4}
0.5	—	3.49×10^{-3}
1.0	1.32×10^{-2}	1.29×10^{-2}
2.0	—	5.00×10^{-2}
5.0	—	3.03×10^{-1}
10.0	1.23×10^{0}	1.20×10^{0}
20.0	—	4.71
50.0	—	24.7

Airborne particles are also removed from the atmosphere by inertial mechanisms. In turbulent inertial deposition, turbulent wind fluctuations perpendicular to a horizontal surface impart sufficient inertia to propel the particles through the boundary layer and onto the surface. This mechanism is important for both smooth and rough surfaces. When the roughness elements on a surface protrude sufficiently far into the windstream, inertial impaction may become important. The mean horizontal flow of the wind, rather than turbulent fluctuations, controls impaction. This mechanism occurs when particles cannot follow the air streamlines as they pass around a roughness element. In this case, the mean windflow supplies the inertia that drives the particles onto the surface.

Inertial mechanisms are dependent on atmospheric conditions and the characteristics of the surface. The small-scale surface structure may be especially significant. For example, small particles are preferentially retained on leaf surfaces, where they may be tightly retained by small hairs on the leaf, by surface pores, and by tacky substances excreted by the leaves. Impaction of submicrometer-sized particles on leaf surfaces is possible at normal wind speeds.[53] Pine needles and similarly shaped surfaces appear to be aerodynamically attractive for impaction of particulate matter. Therefore, pine trees near a surface source of lead particulate pollution may increase the rate at which lead aerosols are removed from the atmosphere. Heichel and Hankin[54] reported soil lead concentrations in front of and within a roadside windbreak of pine trees as being 50 percent and 100 percent higher, respectively, than soil lead concentrations at corresponding distances in a nearby open field that bordered the same side of the road.

Particle removal rates from the atmosphere are usually described in terms of deposition velocity. Historically, deposition velocities have been defined as the ratio of deposition flux to the airborne concentration with units of length/time usually reported as cm/sec.[49] Sehmel and Hodgson[55] have published a model for the prediction of dry deposition velocities based on this concept.

$$K_1 = \frac{N}{C} \qquad (6\text{-}1)$$

where K is the deposition velocity, N is the deposition flux, and C is the airborne concentration for monodispersed particles measured 1 cm above the deposition surface. The deposition velocity, K, assumes that particle deposition is described by a one-dimensional, steady-state continuity equation. The basic assumptions in the model are that the flux is constant with height, that a relationship for particle eddy diffusivity can be determined, that the effect of gravity can be described by the terminal settling velocity, that agglomeration does not occur, and that particles are completely retained on the surface. The model was designed to predict deposition velocities for simple surfaces. Actual removal rates are non-steady-state processes dependent on the delivery capability of the upper atmosphere and the surface resistance. Based on the above assumptions, Sehmel and Hodgson[55] write the equation for deposition flux as:

$$N = -(\epsilon + D)\ \frac{dC}{dz} - v_t C \qquad (6\text{-}2)$$

where v_t is the absolute value of the terminal settling velocity, ϵ is the particle eddy diffusivity, D is the Brownian diffusivity, C is the airborne concentration, and z is the reference height. For small particles, the sedimentation term ($-v_t C$) is negligible so that deposition velocity is a function of the Brownian and eddy diffusivity term only. For large particles, the diffusivity term is negligible, and the deposition velocity is equal to the terminal velocity. Incorporating the concepts of friction velocity:

$$u_* = \frac{u}{K}\,\frac{1}{\mathrm{lm}\,(z/z_0)} \qquad (6\text{-}3)$$

where k is von Karman's constant, u is the windspeed, z is height, and z_0 is the roughness height. Roughness height is defined as a measure of the roughness of a surface over which fluid is flowing:

$$z_0 = H/30 \qquad (6\text{-}4)$$

where H is the average height of surface irregularities. Sehmel and Hodgson[55] developed prediction deposition velocity curves for a range of roughness heights and friction velocities. Representative curves are shown in Figures 6-15 through 6-17. Deposition velocities are shown to be a function of particle diameter and have their smallest values in the 0.1 to 1 μm particle diameter range. The mean diameter of lead-containing particles in the atmosphere, remote from major sources, falls approximately in this range. In the case of larger particles, both increased effective eddy diffusion in surface boundary layer (as a result of greater particle inertia) and increased gravitational settling rates tend to increase the predicted deposition velocities above the minimum. The lower limit of the predicted deposition velocities is the sedimentation velocity. For smaller particles, deposition velocities increase with decreasing particle diameters because of increased mass transfer by Brownian motion. Deposition velocities for 0.01-μm particles are relatively insensitive to changes in particle diameter at elevated heights above 10 cm. Deposition velocities at 1 cm above the ground are extremely large; consequently, in the 0.01-μm particle-diameter range, the deposition velocities are controlled by atmospheric diffusion in the layers immediately above the canopy. As indicated by Sehmel and Hodgson,[55] the model should predict reasonably well the deposition velocities for simple surfaces, assuming the wind direction is persistent over sufficient distance. It should not, however, be expected to predict deposition velocities for a city because of the complexity in the geometry of the surface and because of local wind conditions.

Values of lead deposition velocities found in the literature generally range from about 0.1 to 0.5 cm/sec.[56] These values are based on total lead flux and total airborne concentrations, without regard to particle size. Since large particles may control lead deposition in certain cases, it is necessary to examine the entire size distribution of particles in order to calculate deposition rates. Further, accurate isokinetic measurements of large airborne particles are required to relate airborne concentrations to deposition. Davidson[56] found a deposition velocity of 0.29 cm/sec in Pasadena, based on total flux and total airborne concentrations. Based on the fraction of lead particles greater than 10 microns, however, the deposition velocity was 1.3 cm/sec. Huntzicker et al.[10] found a deposition velocity of 1.80 cm/sec on a Teflon plate placed on the shoulder of a Los Angeles freeway.

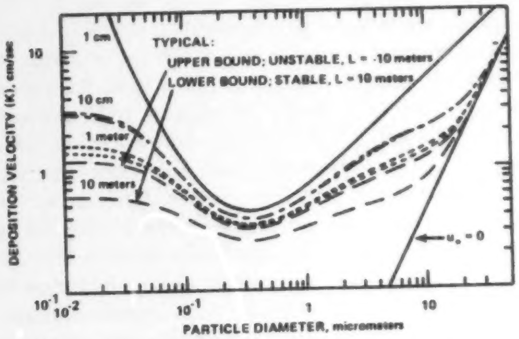

Figure 6-15. Predicted deposition velocity of particles at indicated height for $u_* = 20$ cm/sec and $z_0 = 3.0$ cm.[55]

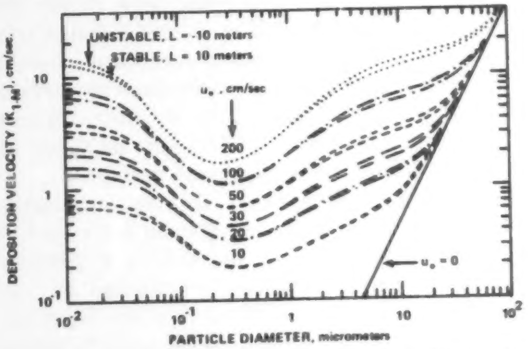

Figure 6-16. Predicted deposition velocities of particles at 1-m height for $z_0 = 3.0$ cm.[55]

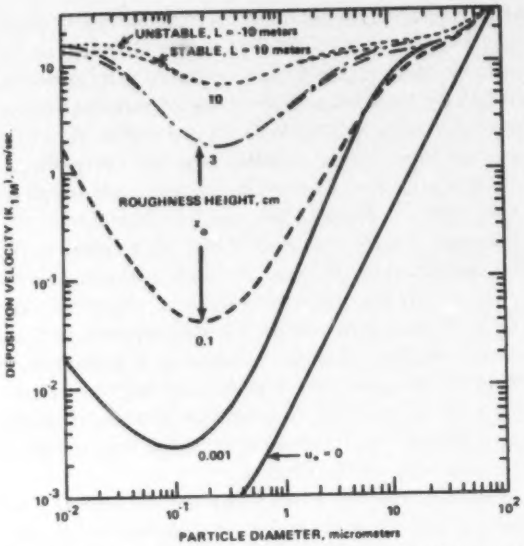

Figure 6-17. Predicted deposition velocities of particles at 1 m for $u_* = 200$ cm/sec.[55]

Johnson[57] sampled particles with an instrumented aircraft flying at 300 m altitude in the vicinty of St. Louis, Missouri. Particles were collected by exposing a small (1.0- by 7.5-cm) glass slide covered with a thin layer of high-viscosity silicone oil to the free air stream outside the skin of the aircraft. Particles were counted and sized manually from photographs. Samples were obtained upwind and downwind of St. Louis on each of 11 days during the period July 1 through July 18, 1975. The results indicated typical number concentrations of airborne particles larger than 10 μm in diameter of 7,500 particles/m^3 upwind and 11,000 particles/m^3 downwind. Particles larger than 30 μm in diameter were found in concentrations of 200 particles/m^3 upwind and 425 particles/m^3 downwind of the city. For the downwind particle number densities of >10 μm and >30 μm particles, and with the assumed density of 2 g/m^3, the mass concentrations would be about 0.01 ng/m^3 and 0.012 ng/m^3, respectively. The results reported indicate that particles >30 μm can be transported to altitudes of 300 m by convective currents; therefore, all large particles are not removed by sedimentation in the immediate vicinity of sources. Assuming a sedimentation velocity of 0.3 cm/sec for a 10 μm-diameter particle and an initial height of 300 m, the particle could remain airborne for approximately 27 hr and be transported about 200 km with a uniform wind of 2 m/sec. This type of long distance transport has been observed by Gillette and Winchester[15] over Lake Michigan. The actual concentrations observed are very small, however, and would contribute little to ambient air loading or dustfall accumulation in regions remote from the source.

Lynam[58] studied the atmospheric diffusion of carbon monoxide and lead from an expressway (I-75, north of Cincinnati, Ohio). The significant results are shown in Figures 6-18 through 6-20. Approximately 50 percent of the lead emitted from the automobile traffic was removed from the atmosphere by dry deposition within 640 ft of the edge of the roadway (Figure 6-18). The size distribution of the lead particles was not significantly altered between 20 and 640 ft (~6 and ~195 meters). Wind speeds ranged from approximately 0.5 to 3.8 m/sec. Assuming a mean wind speed of 2 m/sec, the 50-percent reduction within 640 ft would correspond to about 1.5 min of travel time. The concentration of lead decreased from about 7 $\mu g/m^3$ at 20 ft to about 1.5 $\mu g/m^3$ at 640 ft, a decrease by a factor of about 5. The data were not sufficient to determine the relative efficiency of sedimentation versus impaction in the total removal process; however, Figures 6-19 and 6-20 indicate that the removal mechanism was not strictly limited to sedimentation. Daines et al.,[31] in their study of the relationship of atmospheric lead to traffic volume and distance from a highway, found a 50-percent reduction in lead between 10 and 150 ft of the edge of the roadway.

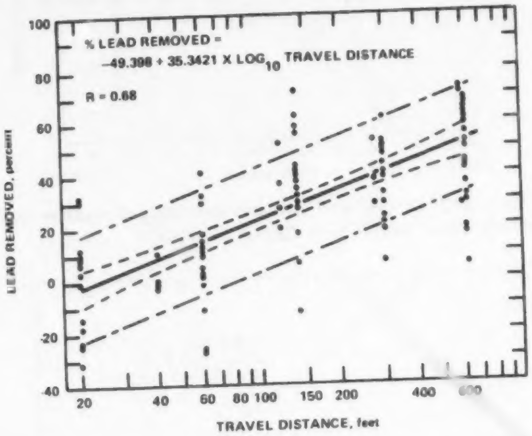

Figure 6-18. Regression of percentage lead particulates removed by dry deposition with distance from roadway.[58] (Legend: —= regression line; ---= 95% confidence limits for regression line; —·—= 95% confidence limits for single value; R = correlation coefficient.)

Smith[59] investigated lead contamination of white pine growing along an east-west section of Interstate 95 in Connecticut. He found that lead contamination decreased regularly with increasing distance from the road and was greatest on the sides of the trees nearest the highway. Based on the much higher concentration of lead deposited on the needles nearest the roadway, Smith concluded that pine trees may serve as rather efficient air filters.

6.3.2.2 PRECIPITATION

Precipitation, or wet deposition, removal processes include rainout and washout. Rainout occurs when particulate matter is present in the supersaturated environment of a growing cloud. The small particles (0.1 to 0.2 μm) act as nuclei for the formation of small droplets, which grow into raindrops.[49] Droplets also collect particles under 0.1 μm by Brownian motion and by the water-vapor gradient. The nucleation process may also occur on particulate matter present below cloud level, producing droplets large enough to be affected by sedimentation. These processes are referred to as rainout. A second process (washout) occurs when falling raindrops collect particles by diffusion and impaction on the way to the ground. Rainout and

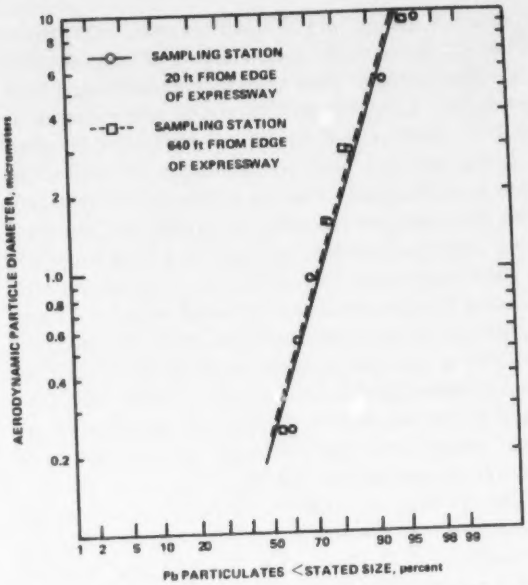

Figure 6-19. Comparison of size distribution of lead particulates collected at 20 and 640 ft from an expressway north of Cincinnati, Ohio. Determined by seven-stage Andersen sampler.[58]

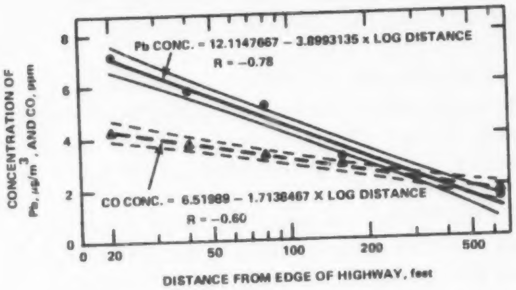

Figure 6-20. Atmospheric concentration of lead and carbon monoxide as a function of log of distance from edge of highway (R = correlation coefficient).[58]

washout together are known as wet deposition. Although data on the lead content of precipitation are rather limited, those that do exist indicate a high variability. Lazrus et al.[60] sampled precipitation at 32 U.S. stations and found a correlation between gasoline use and lead concentration in rainfall in each area. Similarly, there is probably a correlation between lead concentration in rainfall and distance from large stationary point sources of lead emissions in the vicinity of such sources. The authors pointed out that at least twice as much lead is found in precipitation as in water supplies, inferring the existence of a process by which lead is depleted after precipitation reaches the ground. Russian studies[61] point to the insolubility of lead compounds in surface waters and acknowledge this removal by natural sedimentation and filtration.

The intensity of rainfall appears to be negatively correlated with the amount of lead washed out of the atmosphere. Ter Haar et al.[62] found that showers had lower concentrations than slow, even rainfall. Data presented by Jaworowski[44] show that in recent years, the lead content in rainwater ranged from 0 to 1858 μg/liter.

A laboratory study in which simulated rainfall was used to determine the efficiency with which automotive lead particulates could be washed out indicated that the efficiency was less than 1 percent.[63]

Concentrations of ^{210}Pb in rainwater have also been reported by Jaworowski[44] as highly variable (as much as two orders of magnitude in the same locality) and not related to season or amount of precipitation. Values ranged from 0.2 to 300 pCi/liter.[44] High concentrations were found in samples collected from northern continental localities, and low concentrations were found in samples from oceanic and Antarctic locations. Jaworowski suggests that the differences might be attributed in part to artificial contamination by nuclear explosions.

6.3.2.3 FIELD STUDIES

Atkins and Kruger[64] conducted a field sampling program in Palo Alto, California, to determine the effectiveness of sedimentation, impaction, rainout, and washout in removing lead contaminants from the atmosphere. Rainfall in the area averages approximately 33 cm (13 in)/year and occurs primarily during the late fall and winter months. Airborne concentrations at a freeway site varied from 0.3 $\mu g/m^3$ to a maximum of 19 $\mu g/m^3$ in the fall and winter seasons, and were a maximum of 9.3 $\mu g/m^3$ in the spring. During periods of light rainfall in the spring, the maximum concentration observed was 7.4 $\mu g/m^3$. A typical daily concentration profile observed is shown in Figure 6-21. More than 90 percent of the lead pollutants reaching the surface during the 1-year sampling period were collected in dry fallout. Dry deposition as a function of distance from the freeway is shown in Figure 6-22.* Approximately 1 percent of the total dry fallout collected near the expressway was lead. Wet deposition (approximately 33 cm or 13 in of rain per year) accounted for 5 to 10 percent of the lead removal at the sampling sites. A summary of the field data is shown in Table 6-10.

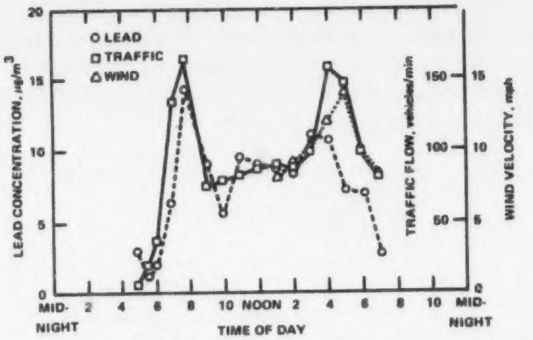

Figure 6-21. Atmospheric lead concentration at freeway site in Palo Alto, California, on August 15, 1966.[63]

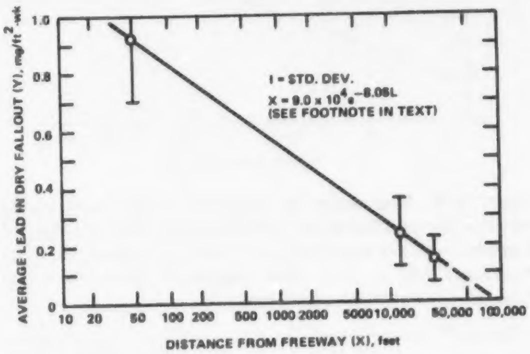

Figure 6-22. Average lead in dry fallout as a function of distance from the freeway.[63]

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*Figure 6-22 is a semi-log plot of the three average lead values as a function of distance from the freeway. The data appear to fall along a straight line, suggesting that the relationship between lead in fall out, L, and distance from the freeway, X, can be described by $X = ae^{bL}$ where a and b are constants. From the semi-plot, the appropriate values for a and b are $a = 9.0 \times 10^4$; $b = -8.06$, if L is expressed in mg/ft^2-wk and X is expressed in feet. Therefore $X = 9.0 \times 10^4 e^{-8.06L}$. The area under this curve, from $X_1 = 50$ ft to $X_3 = 26{,}900$ ft, should represent the total amount of lead deposited in the Palo Alto area for each 1-ft section of freeway. This value is 7.85 g/ft. The area under the curve from $L = 0.95$ mg/ft^2-wk to $L = 0$ should represent the total amount of lead that was removed by sedimentation, assuming that the data can be extrapolated past 26,900 ft. This value is 11.1 g/ft. This indicated that an average of 70 percent of the lead that was removed by sedimentation was removed within 5 miles of the source.

TABLE 6-10. SUMMARY OF FIELD DATA FROM PALO ALTO, CALIFORNIA[64]

Item	Freeway[a] (Bayshore)	Resi-dential	Foot-hills
Lead in dry fallout:			
Average, mg/ft^2-wk	0.92	0.24	0.153
Amount removed, mg/ft^2-yr	49.4	11.7	8.3
Lead in rainfall:			
Average, mg/liter	0.181	0.149	0.035
Amount removed, mg/ft^2-yr	3.25	3.66	0.92
Average air concentration, $\mu g/m^3$	7.30	2.28	1.90
Pb/total solids in air	0.042	0.018	0.016
Pb/nonvolatile solids in dry fallout	0.0112	0.0102	0.0049

Andren et al.[65] evaluated the contribution of wet and dry deposition of lead in a study of the Walker Branch Watershed, Oak Ridge, Tennessee, during the period June 1973 to July 1974. The mean precipitation in the area is approximately 130 cm/year (51 in/year). The major atmospheric emissions in the vicinity of Oak Ridge are derived primarily from three coal-fired steam plants. A foundry and ferroalloy plant approximately 64.5 km (40 miles) to the west were assumed to have a minor impact because of orographic barriers. Results reported for the period January through June of 1974 are presented in Table 6-11. Rainfall, or wet deposition, contributed approximately 67 percent of the total deposition for the period.

TABLE 6-11. DEPOSITION OF LEAD AT THE WALKER BRANCH WATERSHED, 1974[65]

Period	Lead deposition (g/ha)	
	Wet[a]	Dry
January	34.1	< 16.7
February	6.7	< 3.3
March	21.6	< 10.6
April	15.4	< 7.5
May	26.5	< 13.0
June	11.1	< 5.4
Total	115.4	56.5
Average	19.2	9.4

[a] Total deposition ~ 172 g/ha. Wet deposition ~ 67 percent of total.

Huntzicker et al.[10] estimated the flow of automobile-emitted lead in the Los Angeles Basin based on measurements of particle size, atmospheric concentrations, and surface deposition of lead at various sites around the Basin. A flow diagram based on the study and modified by Schuck and Morgan[66] is shown in Figure 6-23. Of the lead emitted from automobile exhaust in the Basin (estimated to be about 18 tons per day), the investigators calculated that about 56 percent was deposited near the source (near deposition), 12 percent was deposited in the Basin but in areas removed from the source (far deposition), and about 32 percent was transported out of the Basin by the wind. The values presented for deposition and wind removal were for dry weather only (i.e., dry deposition only).

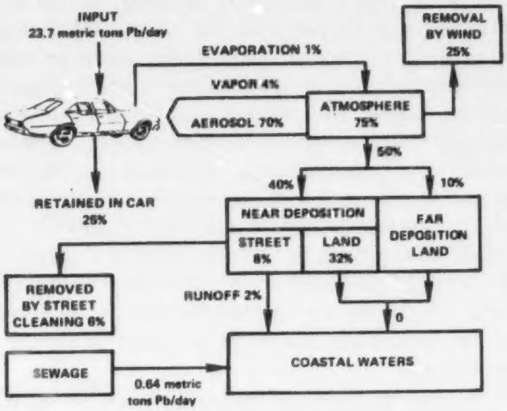

Figure 6-23. Fate of lead contributed from automotive traffic in Los Angeles Basin.[65]

Roberts et al.[67] found an exponential decrease in dustfall with distance around two secondary smelters (Figure 6-24). The authors concluded that the high rate of fallout around the smelters originated from episodal large-particulate emissions from low-level fugitive sources rather than from the stack. This being the case, sedimentation would be the principal removal process. The lead in dustfall values decreased well over 90 percent within a distance of 300m.

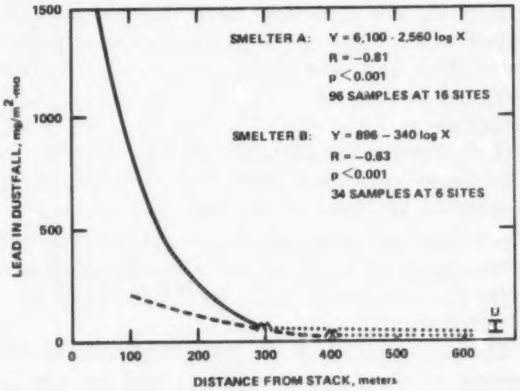

Figure 6-24. Contamination of dust by lead emissions from two secondary smelters. Solid and dashed lines are fitted curves corresponding to the regression equations; dotted lines are an extrapolated fit; U indicates corresponding values found in urban control areas.[66]

Studies such as those described above clearly indicate that lead is effectively removed from the atmosphere by dry and wet deposition processes, and that atmospheric concentrations are significantly influenced by these removal mechanisms even in the immediate vicinity of the source. The rate of removal is highly dependent, however, on the size distribution of the particles, the nature and characteristics of the deposition surfaces, airborne concentrations, and atmospheric conditions including stability, winds, and precipitation. In dry weather, the lead will be deposited on surfaces in the form of dustfall by sedimentation, diffusion, or inertial mechanism, depending primarily on the size of the particles. Mass deposition near the sources will be controlled primarily by sedimentation of large particles, whereas the smaller particles will remain airborne longer, be transported further by the wind, and be removed primarily by diffusion and inertial mechanisms.

The characteristics of the surfaces on which the lead is deposited will significantly influence the deposition and retention. Deposition will be greater in a wooded area than on paved surfaces or short grass. Buildings also will influence the dry deposition, although there are few data available to quantify the effect. In areas with higher annual rainfall, removal by precipitation (wet deposition) becomes more important and may be the dominant process.

All of these factors substantially influence potential human lead-exposure patterns — both inhalation of airborne lead and possible ingestion of dust containing lead. The dry deposition removal mechanisms deplete the airborne concentrations but deposit the material in the form of dust. The factors controlling dry deposition then become extremely important from the standpoint of potential exposure patterns for dust, since they may strongly influence temporal and spatial variations. Because of sedimentation of large particles, dustfall rates (mass) will be highest immediately adjacent to roadways with dense automobile traffic and near stationary sources of all types where lead may be emitted. These rates will diminish to a rather low value in areas remote from sources and where the small particles are removed primarily by diffusion and inertial mechanisms.

The accumulation on the deposition surfaces will depend on the rate of deposition and the rate at which the material is cleaned from the surfaces by precipitation or by mechanical means such as street sweeping or vacuuming. Dust entering buildings or homes by air transport will usually be deposited on flat surfaces such as floors or furniture. The same physical processes will control the rate of deposition. The potential exposure level, particularly for young children, will depend on the accumulation, which again will be influenced by the deposition rate and the frequency and methods of cleaning. In occupational environments where fugitive dust emissions are high, accumulation will be rapid if surfaces are not frequently cleaned. Significant amounts of this dust may be carried on clothing into the homes of workers and contribute further to the total lead-dust loading in the home environment.

Emission rates from automobile traffic and from stationary sources are highly variable in time, even on an hourly basis. Since the residence time of large particles in the atmosphere is on the same order or less, the dustfall rates in the immediate vicinity of sources should also be highly variable. This is reflected in airborne concentrations measured very near the source.

As a consequence of the number of variables involved and of the temporal and spatial variations occurring, it is not possible to quantify human exposure in uncontrolled cases without the use of personal monitors. Estimates of such exposure may vary by an order of magnitude or greater. For a given emission pattern, one can generally conclude that potential exposure from lead in dust should be greatest (1) in dry seasons, (2) in areas with sparse vegetation, (3) within a few hundred meters of the sources, (4) under conditions of stable atmospheres, (5) during the morning and afternoon traffic rush hours in the vicinity of freeways, and (6) during peak production periods of stationary sources (usually during the day).

6.3.2.4 RESUSPENSION

The threshold stress, which must be exceeded before a particle is resuspended from a surface, is a function of the particle properties, particle size, and the surface properties. A particle of a given size and density will resuspend more easily from a smooth surface than from an irregular surface such as an asphalt road. Particles on a dirt road or other soil surfaces may become attached to soil particles and behave quite differently from an inert free particle. This process of weathering tends to reduce resuspension. Moisture, influenced by atmospheric variables such as wind, precipitation, humidity, and solar radiation, may inhibit resuspension.

Data in the literature on resuspension show that this process is not well understood, and hence resuspension rates cannot yet be predicted to any degree of accuracy. For example, Mishima[68] indicates that reported resuspension factors* vary over 10 orders of magnitude from 10^{-2} to 10^{-11}. (The resuspension factor, in m^{-1}, equals the airborne concentration, in ng/m^3, divided by the ground source concentration, in ng/m^2.) It is useful, however, to examine data from more controlled resuspension experiments in order to obtain a qualitative idea of expected lead resuspension rates.

Sehmel[69] has examined the resuspension of ZnS particles smaller than 25 microns from an asphalt road surface. He found that when a car was driven across the recently applied tracer, 0.001 percent to 1.0 percent of the material was resuspended. However, the fraction resuspended decreased by 2 to 3 orders of magnitude when a 30-day period elapsed between application of the tracer and the car passage.

The fraction resuspended per vehicle passage increased as a function of vehicle speed and was independent of wind velocities for the test conditions. The fraction resuspended per vehicle passage was greater for a drive through the tracer test lane than on the adjacent lane and greater for a 3/4-ton truck than for a car. These results suggest that resuspension of lead from roadways may play a significant role in the overall transport of lead away from automotive sources. This may be important considering the conclusions of Huntzicker et al.[10] that a considerable fraction of the emitted lead deposits directly on the roadways.

In another experiment, Sehmel and Lloyd[70] examined the resuspension of 10-μm monodisperse uranine particles from a smooth surface in the laboratory. They found that the fraction of material resuspended per second varied from 10^{-6} to 10^{-3} for wind speeds of 16.5 to 18.3 m/sec. They also measured the resuspension of $CaMo_4$ over sandy soil.[70] The fraction of material resuspended per second ranged from 2×10^{-10} to 2.2×10^{-8} for winds of 1.3 to 20 m/sec.

A limited amount of data on lead resuspension is also available. Figure 6-25 shows the deposition of lead found as a function of height above a roof surface.[72] The lead was deposited on flat Teflon plates mounted at various heights. The greater depositions close to the roof are believed by the investigators to be due to resuspended roof dust.

The environmental consequence of salt particle resuspension from roads has been reported by Smith.[73] Needles from white pine planted adjacent to an interstate highway in Connecticut showed excessive sodium and calcium content resulting from airborne salt resuspension from the highway. The deposition of airborne salt appears to be similar to that of lead from automobile exhaust.[69]

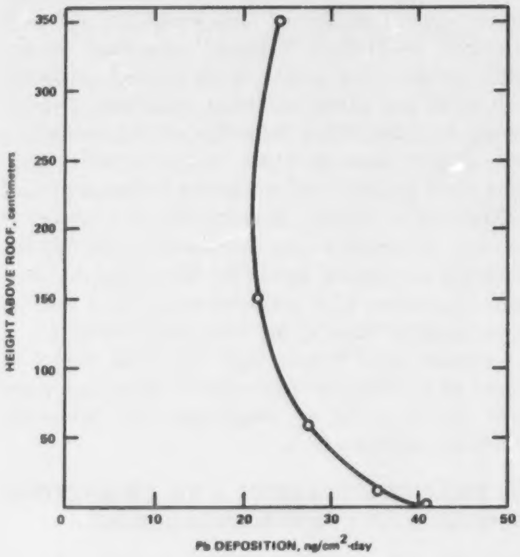

Figure 6-25. Total deposition of lead on Teflon plates at various heights above the roof of Keck Laboratories, California Institute of Technology, Pasadena.[71]

Baum et al.[74] sampled airborne particulate for a period of about 2 years at several locations in Portland, Oregon, using paraffin-coated Mylar films with four- and five-stage Lundgren impactors. Soil and dust samples, both surface and subsurface, were also taken at the air-sampling sites. Samples were analyzed for lead and other elements. Chemical elemental balance methods were used to calculate soil and dust burdens in the air. The authors report that greater than 90 percent of the submicrometer-sized airborne particles were associated with automotive emissions. The larger particles were reported to be contributed about equally by resuspended street dust and direct emissions from automobiles.

These data suggest that lead resuspension may play an important role in the transport of lead. At present, however, it is not possible to reach quantitative conclusions about this mechanism. Size distribution measurements of ambient lead presented here and elsewhere in the literature represent airborne data that have been influenced by the combined factors of atmospheric transport, deposition, and resuspension.

6.3.3 Models

There is an extensive body of literature on atmospheric transport and diffusion models.[75-79] A detailed discussion is beyond the scope of this document. The mathematical models are usually based on the basic Gaussian plume model emanating from the early work of Sutton[46] and Pasquill[47] and well described by Gifford.[76] Stern[77] provided an excellent review of air quality modeling techniques for both rural and urban modeling situations. Experimental data describing the pollutant concentrations from point sources show that, in spite of wide variations, these plumes exhibit a strong tendency toward a Gaussian or normal distribution as a statistical average. In simple terms, parameters reflecting the turbulent component define the horizontal and vertical dimensions of a pollutant cloud in a vertical plane perpendicular to the mean wind velocity.

Cermack et al.[80] have used the wind tunnel to model physically the atmospheric boundary layer over urban areas to determine the pollutant transport characteristics.

6.4 TRANSFORMATION AND TRANSPORT IN OTHER ENVIRONMENTAL MEDIA

6.4.1 Soils

Numerous studies have shown significant contamination of soils by the emission of lead from mobile and stationary sources and through the disposal of waste products. Excellent reviews of the early literature, as well as reports on more recent research, have been published by members of a joint research staff from Colorado State University and the Universities of Missouri and Illinois.[20,29] Many of the studies of lead before 1973 were limited to analysis for elemental lead and did not include analysis for associated ions. Such information is not sufficient to permit a thorough examination and understanding of (1) transformation and transport processes that occur among the environmental media, (2) mobility of lead in soils, (3) uptake and distribution of lead in plants, and (4) the overall impact of lead on human health and ecosystems. Information on the chemical forms of lead is needed.

Soil is a complex matrix composed of several hundred different compounds, only a small fraction of which are lead. Most analytical techniques are not capable of providing positive identification of specific compounds unless separation methods are used that do not alter the lead compounds. Recently, nondestructive separation/preconcentration techniques have been developed and used by the Colorado State University research group to determine lead compounds in soil and plants.[10]

Lead contaminants are deposited on soil by dry and wet deposition processes. Present understanding of the chemical reactions involving these particles once they are deposited into or on the soil is incomplete.[81] Early work indicates that lead probably reacts with soil anions, e.g., $SO_4^=$, $PO_4^=$, or $CO_3^=$, or with some organic or clay complex.[82] These reactions would tend to make the Pb insoluble, thus inhibiting rapid mobility in the soil or plant as well as microbial uptake. Direct evidence supporting these reactions is limited. In a study by Lagerwerff and Brower,[83] lead was precipitated in Na^+-treated, alkalized soils. The solubility of the precipitate increased with decreasing pH and concentration of NaCl. Furthermore, absorption of soil lead by hydrous oxides of iron and manganese, and its consequent immobilization, has been reported by Gadde and Laitinen.[84]

Studies have identified cation exchange capacity, organic matter content, pH, soil type, and soil drainage as the important factors influencing the mobility of lead in soils.[85] Santillan-Medrano and Jurinak[86] conducted batch equilibrium studies to obtain solubility data for lead and cadmium in soil. Lead solubility decreased in the soils as pH increased. The lowest values were obtained in calcareous soil. In noncalcareous soil, the solubility of lead appears to be regulated by $Pb(OH)_2$, $Pb_3(PO)_4)_2$, $Pb_4O(PO_4)_2$, $Pb_5(PO_4)_3OH$, and even $PbCO_3$, depending on the pH.

The creation of organic chelating agents by biologic activity serves as one of the most effective processes of metal mobilization or immobilization in the soil. These agents are either plant products, microbial metabolities, or humic compounds (humic acids). The latter are capable of precipitating lead. The amounts and types of organic matter present appear to provide an important control mechanism for the movement of heavy-metal ions in soil systems. The association of lead and organic matter, however, is not always empirically consistent.[87]

Olson and Skogerboe[29] preconcentrated lead compounds in roadside soil samples and used X-ray powder diffraction techniques for compound identification. The lead compounds in each soil fraction examined are shown in Table 6-12. The most abundant lead salt found was the relatively insoluble $PbSo_4$. The authors note that generally 70 percent or more of the total lead in the soils examined was contained in the dense fractions and that the majority (>50 percent) of this lead was present as sulfate. The results indicate that oxides present in the soil were minor constituents compared to the sulfate concentrations. Since lead bromochloride compounds are the principal constituents of fresh automobile exhaust emissions, conversion to lead sulfate must have occurred either in the atmosphere or in the soil. The authors suggest that sulfuric acid formed from SO_2 in the atmosphere or at the soil interface may react with the lead particulate to form lead sulfate. Reaction with the sulfate ion also may occur in the soil in contact with groundwater.[24] The results of Lee et al.[9] (Section 6.2.2.1) support these general contentions.

Data are limited regarding the chemical composition of lead in soil contaminated by emissions from stationary sources. Lead sulfide and lead chloride are thought to be the major constituents in soils in the vicinity of mining industries, and lead oxide is the chief one in the vicinity of smelters. The presence of lead sulfide as the primary compound in soils along a mine-access road in Missouri has been reported, (Table 6-12). Analytical data confirming the other compounds mentioned above are not available.

6.4.2 **Water**

6.4.2.1 INORGANIC

The chemistry of lead in an aqueous solution is highly complex because the element can be found in a multiplicity of forms. Hem and Durum have reivewed the chemistry of lead in water in detail,[88] and the aspects of aqueous lead chemistry that are germane to this document are discussed in Chapter 3.

Natural concentrations of lead in lead-ore deposits do not normally move appreciably in ground or surface water. Any lead dissolved from primary lead sulfide ore tends to combine with carbonate or sulfate ions to (1) form insoluble lead carbonate or lead sulfate, or (2) be absorbed by ferric hydroxide.[87] An outstanding characteristic of lead is its tendency to form compounds of low solubility with the major anions of natural water. The hydroxide, carbonate, sulfide, and more rarely the sulfate may act as solubility controls. The amount of lead that can remain in solution in water is a function of the pH of the water and the dissolved salt content. Equilibrium calculations show that the total solubility of lead in hard water (pH >5.4) is about 30 μg/liter and about 500 μg/liter in soft water (pH <5.4).[89] Lead sulfate ($PbSO_4$) is present in soft water and limits the lead concentration in solution. Above pH 5.4, $PbCO_3$ and $Pb_2(OH)_2CO_3$ limit the concentration. The carbonate concentration is in turn dependent on the partial pressure of CO_2 as well as the pH. Calculations by Hem and Durum[88] show that many river waters in the United States have lead concentrations near the solubility limits imposed by their pH levels and contents of dissolved CO_2 species. Because the influence of changing temperature and pH may be substantial, observed lead concentrations may vary significantly from theoretically calculated ones.

TABLE 6-12. LEAD COMPOUNDS IDENTIFIED IN ROADSIDE SOILS BY X-RAY POWDER DIFFRACTION TECHNIQUES[29]

Location and soil fraction	Compounds found	Estimated concentrations[a]
Fort Collins:		
Magnetic	$PbSO_4$	Major
Nonmagnetic	$PbSO_4$	Major
	$PbO \cdot PbSO_4$	Minor
	PbO_2	Trace
	PbO[b]	Trace
Denver:		
Magnetic	$PbSO_4$	Major
Nonmagnetic	$PbSO_4$	Major
Chicago:		
Magnetic	$PbSO_4$	Major
Nonmagnetic	PbO	Major
	$PbSO_4$	Minor
Chicago:		
Magnetic	$PbSO_4$	Major
Nonmagnetic	$PbSO_4$	Major
Missouri:		
Magnetic	None[c]	——
Nonmagnetic	PbS	Major
	$PbSO_4$	Minor

[a] Major indicates the principal portion of lead present in the soil fraction indicated and, therefore, the principal portion of the soil sample. Minor refers to approximately 1 to 10 percent of the lead in the respective fractions. Trace quantities are less than approximately 1 percent of the total in each fraction.

[b] Assignment is based on the presence of only the most intense d-spacing and is therefore questionable.

[c] Complex d-spacing pattern obtained with all intensities low; positive assignment of any one compound or group of compounds is questionable.

Lazrus et al.[60] calculated that as much as 138 g/ha-mo of lead may be deposited by rainfall in some parts of the northeastern United States. Assuming an average annual rainfall runoff of 50 cm (~20 in), the average concentration of lead in the runoff would have to be about 330 μg/liter to remove the lead at the rate of 138 g/ha-mo. Concentrations as high as 330 μg/liter could be stable in water with pH near 6.5 and an alkalinity of about 25 ng bicarbonate ion/liter of water. Water having these properties is common in runoff areas of New York State and New England; hence, the potential for high lead concentrations exists there. In other areas, the average pH and alkalinity are so high that less than 1 μg/liter of lead could be retained in solutions at equilibrium.[87]

A significant fraction of the lead carried by river water may be in an undissolved state. This nonsolute lead can consist of colloidal particles in suspension or larger undissolved particles of lead carbonate, oxide, hydroxide, or other lead compounds incorporated in other components of particulate lead from runoff, either as sorbed ions or surface coatings on sediment mineral particles or carried as a part of suspended living or nonliving organic matter.[87] A laboratory study by Hem[90] of sorption of lead by cation exchange indicated that a major part of the lead in stream water may be adsorbed on suspended sediment. Figure 6-26 illustrates the distribution of lead outputs between filtrate and solids in stream water from both urban and rural compartments, as reported by Rolfe and Jennett.[91] The majority of lead output is associated with suspended solids in both urban and rural compartments with very little dissolved in the filtrate. The ratio of lead in suspended solids to lead in filtrate varies from 4:1 in the rural compartment to 27:1 in the urban compartment.

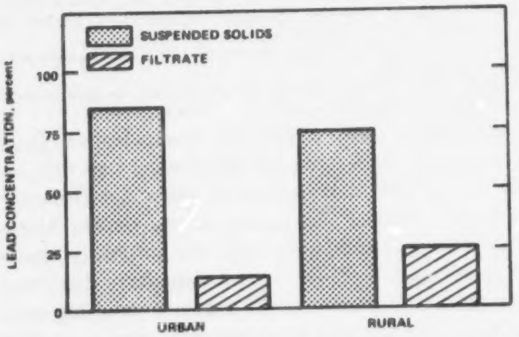

Figure 6-26. Lead distribution between filtrate and suspended solids in stream water from urban and rural compartments.[90]

The concentration of lead usually reported represents a somewhat arbitrarily defined solute fraction, separated from the nonsolute fraction by filtration. Most filtration techniques cannot be relied on to remove all colloidal-sized particles. Upon acidification of the filtered sample, which is usually done to preserve it before analysis, the colloidal material that passes through is dissolved and reported in that form. Usually the solids removed from a surface water sample by filtration are not analyzed for lead. But even the lead in rainfall can be mainly particulate, and thus it will be necessary to obtain more information on the amounts of lead transported in nonsolute form[87] before a valid estimate can be obtained of the effectiveness of runoff in transporting lead away from areas where it has been deposited by atmospheric fallout and rain.

6.4.2.2 ORGANIC

The organic components of soil-water system are an extremely diverse group of compounds that includes carbohydrates, amino acids, phenolic and quinonic compounds, organic acids, nucleic acids, enzymes, porphyrins, and humic materials.[87] In addition to the natural organic compounds present in soils, streams and lakes contain organic sediments and suspended solids that have been derived from municipal, agricultural, and industrial wastes. These wastes include carbohydrates, proteins, nucleic acids, enzymes, lipids, and many other organic compounds found in living systems. In addition, oils, plasticizers, polymers, and many other organic compounds are discharged to natural waterways by manufacturing and chemical industries. The interaction of lead with these organic compounds is still not well understood, but most of these organic materials can confidently be expected to form complexes with lead (and other metals), since they all contain available donor sites for complexation. A discussion of metal complexation is presented in Chapter 3 and Appendix B.

The presence of fulvic acid (a constituent of soil humic materials) in water has been shown to increase the rate of solution of lead sulfide 10 to 60 times over that of a water solution at the same pH that did not contain fulvic acid.[87,92] At pH values near 7, soluble lead-fulvic acid complexes were present in solution. At initial pH values between 7.4 and about 9, the lead-fulvic complexes partially decomposed, and lead hydroxide and carbonate were precipitated. At initial pH values of about 10, the lead-fulvic acid complexes again increased. This increase was attributed to dissociation of phenolic groups at high pH values, which increases the complexing capacity of the fulvic acid. But it may also have been due to the formation of soluble lead-hydroxyl complexes.

In summary, the complexing of lead by most of the common sulfur-, phosphorus-, oxygen-, and nitrogen-containing ligands means that lead will accumulate in living and nonliving organic components of soil-water and sediment-water systems. The living and nonliving organic components are not independent of each other, but they are constantly interacting as the living components metabolize the nonliving components of the system and then die, contributing their remains to the pool of nonliving compounds in the system. The fate of heavy metals in this process has not been elucidated; but the sediment in a contaminated surface-water body will serve as a large reservoir that can provide lead and other metals to the biota of the system even after heavy-metal pollutants have ceased to be introduced. Most attention has been given to the heavy metals dissolved in the water phase of surface water rather than to the complexed metals in the sediment phase, though sediments probably contain a higher amount of lead.[87]

The biotransformation of lead to volatile tetramethyl lead constitutes one mechanism by which lead may leave sediment-water systems. The direct, biological methylation of certain inorganic lead compounds by lake sediment microorganisms has been reported.[93,94] All the lake sediments tested were able to transform trimethyl lead to tetramethyl lead,[93] but only some of the sediments were able to transform lead nitrate and lead chloride into tetramethyl lead. No biotransformation occurred when the lake sediments were incubated with lead oxide, lead hydroxide, lead bromide, lead cyanide, or lead palmitate.[93] Certain pure bacterial isolates (see Chapter 8) from these lake sediments were shown to transform trimethyl lead to tetramethyl lead in the anaerobic incubation system used.[93]

The conversion of the tri- to the tetramethyl lead salt was subsequently postulated to be chemical rather than biological, proceeding via formation and then decomposition of an organic sulfide intermediate, $(Me_3Pb)_2S$.[95] Using a system containing no sulfides, however, other workers showed the production by microorganisms of Me_4Pb from Me_3Pb^+ much in excess of yields expected from the stoichiometry of redistribution reactions of lead alkyl compounds in aqueous solutions.[94] Thus, the alkylation appears to be direct and biological. The alkylation of lead, unlike that of mercury, was not mediated by methylcobalamin, as shown when equimolar amounts of Me_3PbOAc, Me_3PbCl, Me_2PbCl_2, and $Pb(NO_3)_2$ were substituted for inorganic mercury in an aqueous test system (~pH 7).[95] Taylor and Hanna,[96] however, have recently demonstrated that prolonged incubation of methylcobalamin with a fine suspension of lead oxide (Pb_3O_4) in an aqueous medium results in partial demethylation of the corrinoid. This chemical demethylation of MeB_{12} by Pb_3O_4 was shown to be highly pH dependent, with no demethylation occurring at pH 7, and 61 percent occurring at pH 2. Tracer studies with [^{14}C]-methyl-labeled methylcobalamin indicated that demethylation of MeB_{12} by Pb(IV) was accompanied by a proportional volatilization of the label. These results are in agreement with the known instability of monoalkyl lead compounds in aqueous media as described by Wood.[97]

The alkylation of lead, then, unlike that of mercury, does not appear to result in nonvolatile, toxic organolead that could undergo biomagnification in the food chain. Volatile TML generated *in situ* would be expected to escape from a body of water. The possible uptake of tetramethyl lead by aquatic organisms during its passage to the surface of a body of water is unknown.

6.4.3 **Plants**

Lead is transferred from the atmosphere to the soil and vegetative compartments of the environment by dry and wet deposition. Considerable attention has been devoted to determining the amount and localization of lead in roadside and smelter areas, but little information is available regarding its chemistry and effects in those areas. Motto el al.[98] suggested that plant uptake is probably related better to soluble rather than total lead in soils. Wilson and Cline[99] concluded that only 0.003 to 0.005 percent of total lead in soil is available for plant uptake. The soil solution is affected by all the reactions that occur as the constituents are changed through addition to or depletion from the soil. Ultimately, the composition of the soil solution is controlled by the solubility of the various mineral phases in the soil. The long-term effects of lead in soils are uncertain. Only recently has attention been given to the solubility relationships of $PbSO_4$, $Pb_3(PO_4)_2$, and $PbCO_3$ as possible controlling mechanisms for the amount of lead in soils.[44] If $PbCO_3$ is involved as a reaction product, there is the possibility that soils of high pH, upon becoming acidic, could release lead at some future time.[100] The question of chemical identity of lead in plants is still largely unanswered. Hamp and Ziegler[101] have suggested that lead associated with plant surfaces in nature may be largely lead phosphate. Zimdahl,[102] citing studies conducted at Colorado State University and the University of Illinois, reported the identification of lead pyrophosphate in bean roots and lead orthophosphate in soybean root. The results of later solubility studies of the two compounds suggested that lead pyrophosphate should be the dominant form in plants.

The process by which lead is taken up by plants, which may be passive,[85,103] is favored under conditions of low soil pH.[104] MacLean et al.[105] have suggested that soil management practices such as the addition of organic matter, lime, and phosphate may be appropriate in contaminated soils to reduce the availability of lead for plant uptake. They found that the concentration in oats and alfalfa varied inversely with pH and organic matter, and that addition of phosphate reduced the uptake of lead; they suggested that the pH effect was due to repression of lead solubility at the higher pH values. John and Van Laerhoven[106] found little difference in uptake by oats and lettuce when lead was derived from water-insoluble lead carbonate as opposed to the more water-soluble lead chloride or nitrate. Hence the formation of lead carbonate as a result of liming would not explain the pH effect.

Work at the University of Illinois and at Colorado State University, cited by Zimdahl,[102] has shown that uptake by several plant species is inversely proportional to soil lead content and is greatest under conditions of low pH and low phosphorus. The binding or exchange capacity of soils, related to organic content, is extremely important as a determinant of lead availability to plants. Chelating agents can modify the uptake and possibly the movement of heavy metals by plants, but the relative importance of natural chelating substances is hard to evaluate at this time.[102] Zimdahl,[102] citing a number of studies regarding chelation of lead with EDTA, concludes that the extent of lead movement within the plant is still unresolved. He questions whether studies with synthetic and highly ionized chelating agents such as EDTA actually reflect what is happening in nature.

In a study conducted at the University of Illinois[107] (cited by Zimdahl[102]), it was shown that the roots of hydroponically grown corn acquired a surface lead precipitate and slowly accumulated crystalline lead in the cell walls. The surface precipitate formed quickly and independently of plant activity. Two compounds were postulated but not identified. The lead entering the root was concentrated in some but not all dictyosome vesicles. After precipitation had occurred in the dictyosome vesicle, cell-wall precursors were added to the vesicle by apposition of vesicles or by internal secretion. As the lead-containing crystals grew, more cell-wall material was added, so that the entire vesicle eventually moved to the periphery of the cell to achieve fusion with the cell wall. Lead deposits were thereby concentrated at the cell wall and not within mitochondria or other organelles.[102] Although this sequence of events was observed in the root tips, deposits were observed throughout the plant, and it was suggested that a similar process occurred in all plant tissues.[102]

The deposition of lead on the leaf surfaces of plants where the particles are often retained for long time periods must also be considered.[32,108,109] Several studies have shown that plants near roadways exhibit considerably higher levels of lead than those farther away. In most instances, the higher concentrations were due to lead particle deposition on plant surfaces.[32] Studies have shown that particles deposited on plant surfaces are often very difficult to remove completely by simple washing techniques considered characteristic of the treatment that would be used in a household kitchen.[108,110,111] Leaves with hairy surfaces seem able to retain (and attract) particles via an electrostatic mechanism. Other types of leaves are covered with a cuticular wax sufficiently sticky to preclude the removal of particles. Thus rainfall does not serve as a particularly effective means of removing the deposited particles.[110] Animals or humans consuming the leafy portions of such plants can certainly be exposed to higher than normal levels of lead. Fortunately, a major fraction of lead emitted by automobiles is deposited inside a typical highway right-of-way, so at least part of this problem is alleviated.

The particle deposition on leaves has led some investigators to stipulate that lead may enter plants through the leaves. This would typically require, however, that the lead particles be dissolved by constituents of the leaf surface and/or converted to the ionic form via contact with water. The former possibility is not considered likely, since cuticular waxes are relatively inert chemically. Zimdahl and Arvik[85] have shown in a rather elegant set of experiments that entry of ionic lead through plant leaves is of minimal importance. By using the leaf cuticles of several types of plants essentially as membranes, they found that even high concentrations of lead ions would not pass through the cuticles into distilled water on the opposite side.

The results of the studies discussed above generally indicate the following:

1. The uptake of lead by plants from soil is highly dependent on the chemical equilibria prevalent in the soil in question. The uptake can probably be controlled through treatment of the soil with materials (e.g., lime, phosphate fertilizers, etc.) that affect these chemical equilibria.
2. Although uptake rates are enhanced at lower soil pH levels, the majority of the lead taken up remains in the plant roots; only smaller fractions are translocated to the shoots.
3. Deposition and retention of lead particles on plant surfaces can serve as a route of animal or human exposure to automotive lead. Thus crops grown near sources of high traffic

should probably be considered suspect unless appropriate safety precautions are taken.

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7. ENVIRONMENTAL CONCENTRATIONS AND POTENTIAL EXPOSURES

7.1 AMBIENT AIR EXPOSURES

Several studies on concentrations of lead in the ambient air have been undertaken. These studies were generally intended to survey the levels and distributions of lead in the general air environment and around sources. They usually were not designed in conjunction with epidemiological studies of the concurrent effects of lead on man or other organisms. Yet that is the context in which these studies must now be interpreted to shed the most light possible on the concentrations likely to be encountered in various environmental settings.

Measurements taken with high-volume samplers, dust-fall buckets, and particle size fractionators are included in these studies; however, with the exception of the NASN data from 1970 through 1974, quality control and interlaboratory comparability are unspecified. The effectiveness of some filter media in collecting very small lead-containing particles has been questioned; this subject is discussed in Chapter 4. The studies show that:

1. Lead typically occurs in urban airborne suspended particles 0.5 μm or less in mass median equivalent diameter at annual average concentrations ranging from <0.1 to 5 $\mu g/m^3$, with an overall average of 1 to 2 $\mu g/m^3$.
2. Urban concentrations of lead have declined somewhat since 1970.
3. Suspended particles in rural air samples contain lead at concentrations ranging from <0.01 to 1.4 $\mu g/m^3$, with an overall average of about 0.2 $\mu g/m^3$.
4. Monthly average concentrations of lead in urban settleable particles range from 3 to 12 mg/m^2-mo.
5. Indoor concentrations of lead are quite variable, but are generally one- to two-thirds the concentrations of adjacent outdoor levels.

A discussion of the NASN measurements follows. Summaries of additional studies can be found in Appendix C.

7.1.1 National Air Surveillance Network (NASN) Data

Since 1957, samples of suspended particulate matter collected at some 300 urban and 30 nonurban NASN sites have been analyzed for trace metals, including lead. Only data beginning with 1966 are summarized here, however, because the procedure used before 1966 was found to recover only about 50 percent of the lead actually present. The emission spectrographic method now employed in the analysis has sufficient sensitivity to permit detection of lead in all urban and most nonurban samples.

Summaries of the data for urban and nonurban NASN sites for 1966 through 1974 are presented in Tables 7-1 and 7-2, which categorize the sites by four successive annual average concentration ranges.[1,2] The majority of the urban sites (91 percent of the site-years) reported annual averages below 2.0 $\mu g/m^3$, and the majority of nonurban sites (86 percent of the site-years) reported annual averages below 0.2 $\mu g/m^3$.

Samples collected by the NASN from 1970 through 1974 were combined for analysis into quarterly composites. Tables 7-3 and 7-4, respectively, give the cumulative frequency distributions of urban and nonurban quarterly composite values for 1970 through 1974.[1]

Urban NASN sites for which annual average concentrations have been 3.0 $\mu g/m^3$ or greater are listed in Table 7-5.[1,2] Highest concentrations for shorter intervals (quarterly and 24-hr) have been included, where available, in order to indicate the variation in concentration with averaging time and potential peak exposure conditions. A large number of Southern California cities are included in the list because of the heavy automobile traffic in these areas. Both the annual average and maximum values at Los Angeles County sites were consistently high,

TABLE 7-1. NUMBER OF NASN URBAN STATIONS WHOSE DATA FALL WITHIN SELECTED ANNUAL AVERAGE LEAD CONCENTRATION INTERVALS, 1966-1974[1,2]

Year	Concentration interval, μg/m³					
	< 0.5	0.5-0.99	1.0-1.9	2.0-3.9	4.0-5.3	Total
1966:						
No. stations	9	40	40	6	—	95
Percent	9	42	42	6	—	100
1967:						
No. stations	4	37	63	9	—	113
Percent	3	32	55	7	—	100
1968:						
No. stations	14	67	54	10	1	146
Percent	9	45	36	6	1	100
1969:						
No. stations	5	46	103	23	1	178
Percent	2	25	57	12	1	100
1970:						
No. stations	9	54	80	15	1	159
Percent	5	33	50	9	1	100
1971:						
No. stations	—	23	64	21	1	109
Percent	—	21	58	19	1	100
1972:						
No. stations	16	67	84	12	1	180
Percent	9	37	47	7	0	100
1973:						
No. stations	20	76	36	4	1	137
Percent	15	55	26	3	1	100
1974:						
No. stations	19	69	38	4	0	130
Percent	15	53	29	3	0	100
1966-1974:						
No. stations	96	479	562	104	6	1247
Total percent	8	38	45	8	1	100

TABLE 7-2. NUMBER OF NASN NONURBAN STATIONS WHOSE DATA FALL WITHIN SELECTED ANNUAL AVERAGE LEAD CONCENTRATION INTERVALS, 1966-1974[1,2]

Year	Concentration interval, μg/m³				
	< 0.03	0.03-0.099	0.10-0.19	0.20-0.45	Total
1966:					
No. stations	—	10	6	3	19
Percent	—	52	32	16	100
1967:					
No. stations	1	7	10	2	20
Percent	5	35	50	10	100
1968:					
No. stations	1	15	4	—	20
Percent	5	75	20	—	100
1969:					
No. stations	—	11	9	1	21
Percent	—	52	43	5	100
1970-1971:					
No. stations	—	—	7	3	10
Percent	—	—	70	30	100
1972:					
No. stations	10	4	9	11	34
Percent	29	12	26	33	100
1973:					
No. stations	9	7	6	1	23
Percent	39	31	26	4	100
1974:					
No. stations	3	5	6	2	16
Percent	19	31	38	12	100
1966-1974:					
No. stations	24	59	57	23	163
Total percent	15	36	35	14	100

TABLE 7-3. CUMULATIVE FREQUENCY DISTRIBUTIONS OF QUARTERLY LEAD MEASUREMENTS AT URBAN STATIONS BY YEAR, 1970 THROUGH 1974[1]
(μg/m³)

Year	No. quarterly composites	Min	Percentile							Max.	Arithmetic		Geometric	
			10	30	50	70	90	95	99		Mean	Std. dev.	Mean	Std. dev.
1970	797	LD[a]	0.47	0.75	1.05	1.37	2.01	2.59	4.14	5.83	1.19	0.80	0.99	1.84
1971	717	LD[a]	0.42	0.71	1.01	1.42	2.21	2.86	4.38	6.31	1.23	0.87	1.00	1.89
1972	708	LD[a]	0.46	0.72	0.97	1.25	1.93	2.57	3.69	6.88	1.13	0.78	0.93	1.87
1973	559	LD[a]	0.35	0.58	0.77	1.05	1.62	2.08	3.03	5.83	0.92	0.64	0.76	1.87
1974	594	0.08	0.36	0.57	0.75	1.00	1.61	1.97	3.16	4.09	0.89	0.57	0.75	1.80

[a] LD = limit of detection.

TABLE 7-4. CUMULATIVE FREQUENCY DISTRIBUTIONS OF QUARTERLY LEAD MEASUREMENTS AT NONURBAN STATIONS BY YEAR, 1970 THROUGH 1974[1]
(μg/m³)

Year	No. quarterly composites	Min	Percentile							Max.	Arithmetic		Geometric	
			10	30	50	70	90	95	99		Mean	Std. dev.	Mean	Std. dev.
1970	124	0.003	0.003	0.003	0.003	0.003	0.267	0.383	0.628	1.471	0.088	0.190	0.040	3.72
1971	85	0.003	0.003	0.003	0.003	0.003	0.127	0.204	0.783	1.134	0.047	0.155	0.008	4.80
1972	137	0.007	0.007	0.007	0.107	0.166	0.294	0.392	0.950	1.048	0.139	0.169	0.090	2.59
1973	100	0.015	0.015	0.015	0.058	0.132	0.233	0.392	0.698	0.939	0.110	0.149	0.068	2.77
1974	79	0.007	0.007	0.053	0.087	0.141	0.221	0.317	0.496	0.534	0.111	0.111	0.083	2.30

TABLE 7-5. NASN STATIONS WITH ANNUAL AVERAGE LEAD CONCENTRATIONS ≥3.0 μg/m³ [1,2]

Year and station	Average	Maximum	
		Quarterly composite	24-hr
1966:			
Phoenix, Ariz.	3.2	8.1	—
Burbank, Calif.	3.7	6.0	—
Los Angeles, Calif.	3.6	11.0	—
Pasadena, Calif.	3.6	4.3	—
1967:			
Los Angeles, Calif.	3.1	5.4	—
1968:			
Burbank, Calif.	4.4	—	14.0
Glendale, Calif.	3.0	—	7.5
Long Beach, Calif.	3.3	—	12.0
Los Angeles, Calif.	3.9	—	10.0
Pasadena, Calif.	3.5	—	8.3
1969:			
Fairbanks, Alaska	3.2	4.8	—
Phoenix, Ariz.	3.1	7.1	—
Burbank, Calif.	3.5	4.7	—
Glendale, Calif.	3.1	4.5	—
Los Angeles, Calif.	4.6	5.7	—
San Juan, Puerto Rico	3.8	4.2	—
Dallas, Tex.	3.0	5.2	—
1970:			
Burbank, Calif.	4.9	5.8	—
Glendale, Calif.	3.5	4.2	—
Los Angeles, Calif.	4.5	5.6	—
San Juan, Puerto Rico	3.7	4.1	—
Dallas, Tex.	3.2	3.8	—
1971:			
Anaheim, Calif.	3.3	4.0	—
Burbank, Calif.	5.3	6.2	—
Santa Ana, Calif.	3.5	4.6	—
Los Angeles, Calif.	4.6	6.3	—
1972:			
Burbank, Calif.	3.2	6.7	—
Glendale, Calif.	3.5	5.2	—
Los Angeles, Calif.	3.1	4.8	—
San Juan, Puerto Rico	5.0	6.9	—
1973:			
Burbank, Calif.	4.0	5-2	—

apparently because of location, topography, and meteorological conditions that favor retention of pollutants in the air over the area.

Ambient particulate lead data from NASN were studied for trends over the 10-year period from 1965 through 1974. Figure 7-1 shows the 10th, 50th, and 90th percentiles for data from 92 NASN urban sites.[3] Urban lead concentrations as described by the 50th percentiles increased from 1965 until 1971 and then declined from about 1.1 μg/m³ to 0.84 μg/m³ — about a 24-percent decrease, with most of this decline occurring between 1972 and 1973. The other percentiles exhibit a similar pattern. This general pattern describes the trend for most of the sites studied. Trends in the percentage of lead in the total particulate matter measured also follow this pattern, which indicates that the trends in lead are not just a result of general particulate controls but are a direct result of decreases in lead emissions.

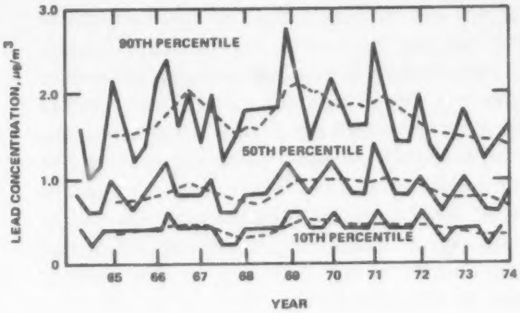

Figure 7-1. Seasonal patterns and trends in quarterly average urban lead concentrations.[3]

The seasonal pattern in quarterly composite values (solid lines in Figure 7-1) shows that the highest levels of airborne lead occurred in the winter quarters (first and fourth) and the lowest levels in the summer quarters (second and third). In contrast, automotive emissions of lead would be expected to be greater in the summer for two reasons: (1) gasoline usage is higher in the summer, and (2) lead content is raised in summer gasolines to replace some of the more volatile high-octane components that cannot be used in summertime gasolines. Evidently summertime meteorological conditions expedite the movement of these larger emissions more quickly and widely through the atmosphere on their way to subsequent destinations in vegetation, crops, soil, and water.

Since about the 1970 model year, automobiles have been built with lower-compression engines that can use lower-octane gasoline and thus gasoline with lower lead content. As a result of this engine modification, practically all cars built since 1970 are able to use regular gasoline instead of the more leaded premium fuels. Figures 7-2 and 7-3 show, respectively, the percentage of the total market for regular and premium gasolines and the trend in lead content of gasolines.[4] The results of the engine modifications can be clearly seen in the lower lead content in gasoline (both in regular and premium grades) and in the subsequent increase in regular gasoline sales and decrease in premium sales. These factors, coupled with the use of a modest amount of low-lead and no-lead gasoline introduced at about this same time, are identified as principally responsible for the observed decrease in ambient lead concentrations over this period. The increasing use of unleaded gasoline resulting from EPA regulations, which is reflected in Figure 7-2, will lead to even lower levels of atmospheric pollution in the future. The effect of these changes is enough to override the general increase in annual gasoline consumption of about 5 percent typical of recent years (except 1974). This increase in gasoline consumption probably does not proportionately affect many urban monitoring sites (which are chiefly center-city locations) because their neighborhoods are generally at or near traffic saturation. There may even be instances of a reduction in vehicle miles traveled in downtown areas because of car pooling, improved mass transit systems, and the loss of business activity to suburban shopping centers.

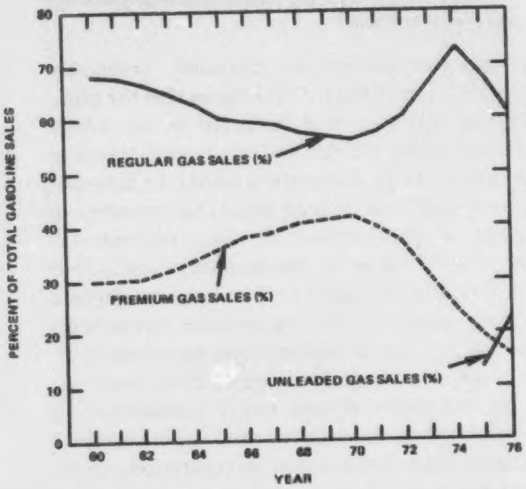

Figure 7-2. Nationwide trends in regular, premium, and unleaded gasoline sales, 1960-1976.[4]

In addition to the NASN study, a number of other studies involving major cities and rural areas have been undertaken. These data support the NASN results (see Appendix C).

7.1.2 Airborne Particle Size Distribution

In 1970, a cascade impactor network was established by EPA in six cities (Cincinnati, Chicago, Denver, Philadelphia, St. Louis, and Washington, D.C.) to collect particulates of different size ranges for subsequent analysis for lead and other metals.[5] The samples, collected once every 2 weeks for a full year, were analyzed for size distribution. Samples from each city were also composited quarterly and analyzed for lead by optical emission spectroscopy.

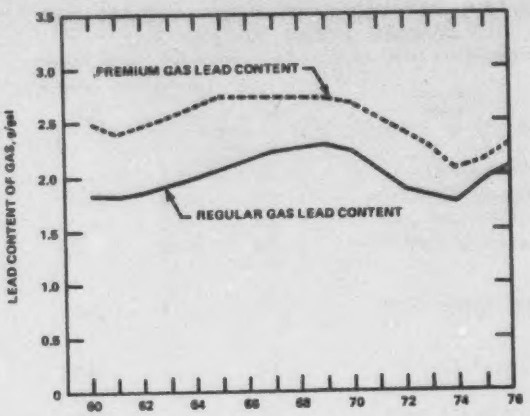

Figure 7-3. Nationwide trends in lead content of regular and premium gasoline, 1960-1976.[4]

The average annual total lead concentration as determined in this study ranged from a high quarter of 3.2 $\mu g/m^3$ in Chicago to a low quarter of 1.3 $\mu g/m^3$ in Washington, D.C. The average mass median diameter for lead particles ranged from 0.69 μm in St. Louis to 0.42 μm in Washington, D.C. Fifty-nine to 74 percent of the lead was associated with particles smaller than 1 μm in diameter. Quarterly and annual particle size distribution data are presented in Table 7-6.

7.1.3 Vertical Gradients of Lead in the Atmosphere

Very few studies have been conducted to determine the variation of lead concentrations with height above the ground. Of those that were found, all contained the premise, either explicitly or implicitly, that the concentrations being studied derived principally from automotive emissions. Of the studies found in the literature, none were adequately designed to establish the lead concentration versus height relationship. Such a study would require simultaneous measurement (preferably continuous) at given height intervals over a long period of time (a minimum of 1 year). Even then, the results would be valid only for a location having the same characteristics and experiencing the same atmospheric conditions. A single set of concentration values obtained over short and variable time intervals is not sufficient to draw conclusions regarding general exposure conditions.

TABLE 7-6. QUARTERLY AND ANNUAL SIZE DISTRIBUTIONS OF LEAD-BEARING PARTICLES FOR SIX CITIES, 1970[a]

City and quarter of year	Average concentration, μg/m³	Average mass median diameter, μm	Percentage of particles ≤ μm
Chicago, Ill.:			
1	2.9	1.43	41
2	3.5	0.51	65
3	3.5	0.56	65
4	2.9	0.54	64
Total year	3.2	0.68	59
Cincinnati, O.:			
1	1.0	0.25	79
2	2.2	0.41	74
3	1.9	0.54	69
4	2.1	0.65	67
Total year	1.8	0.48	72
Denver, Colo.:			
1	2.0	0.43	76
2	1.1	0.58	68
3	1.4	0.52	69
4	3.0	0.56	66
Total year	1.8	0.50	70
Philadelphia, Penn.:			
1	1.5	0.36	74
2	1.2	0.38	74
3	1.8	0.70	62
4	1.9	0.45	70
Total year	1.6	0.47	70
St. Louis, Mo.:			
1	1.9	0.46	68
2	1.6	0.63	63
3	1.8	0.78	59
4	1.8	0.95	53
Total year	1.8	0.69	62
Washington, D.C.:			
1	1.3	0.36	76
2	1.0	0.39	73
3	1.3	0.41	74
4	1.8	0.54	71
Total year	1.3	0.42	74

Darrow and Schroeder[6] measured lead concentrations at eight heights above street level in Brattleboro, Vermont. The values found are shown in Table 7-7. The average traffic flow was reported to be 7500 cars per day. The concentration levels shown in Table 7-7 are considerably higher than those usually reported in other cities. The investigators attributed the higher values to greater collection efficiency and lower sampling heights, but this was not confirmed. The sampling times were short and variable. General conclusions regarding the relationship of concentrations versus height cannot be drawn from these data.

TABLE 7-7. LEAD IN AIR ON MAIN STREET, BRATTLEBORO, VERMONT, SEPTEMBER 12 and 13, 1972[a,6]
(μg/m³)

Height above street, ft	Sampling times				
	8:36 a.m. 10:15 a.m.	10:20 a.m. 12:00 noon	1:20 p.m. 3:00 p.m.	3:25 p.m. 4:25 p.m.	4:35 p.m. 9/12 1:02 p.m. 9/13
1[b]	8.94	7.84	3.85	—	—
2	—	—	5.31	17.38	—
3	8.22	4.40	—	—	—
4	—	—	7.56	21.11	—
5[c]	7.15	8.15	—	—	—
7	—	—	—	2.40	—
8	—	—	—	—	3.01
30	—	—	—	—	4.25

[a] Average air lead value for 54.38 m³ air = 8.54 μg Pb/m³.

[b] 1-, 2-, 3-, and 4-ft heights: Average air lead values for 13.53 m³ air = 8.01 μg Pb/m³.

[c] 5-, 7-, 8-, 30-ft heights: Average air lead values for 40.85 m³ air = 3.96 μg Pb/m³.

Edwards[7] has reported measurements made in downtown Fort Collins, Colo. Measurements were made in a street canyon formed by two- and three-story buildings (average height, 9 m). With a 2.3 m/sec wind from the Northeast (street running north-south), lead concentrations along the east side of the street canyon ranged from 11.3 μg/m³ at street level to 4.0 μg/m³ at roof level. On the west side of the street, concentrations ranged from 0.9 μg/m³ at street level to 1.3 μg/m³ at roof level. Values for two additional sampling points above the rooftops on each side of the street were 0.4 μg/m³ (east side) and 0.9 μg/m³ (west side). Lead concentrations 2 to 5 blocks away ranged from 0.1 to 0.3 μg/m³. These data reflect the wide variability that can be expected in urban traffic environments. Under moderate cross-wind conditions, concentrations within the canyon were strikingly anisotropic, and street-level concentrations along the upwind building faces were substantially higher than along the downwind face. With different wind regimes, different building configuration, and different stability conditions, the distribution of concentration values would also be different.

Barltrop and Strelow[8] conducted an air sampling program at a proposed nursery site under an elevated motorway. The height of the motorway was 9.3 m. Air samplers were operated at five to seven sites from Monday to Friday, 8 a.m. to 6 p.m. for 1 year. The maximum individual value observed was 18 μg/m³. The 12-month mean ranged from 1.51 μg/m³ to 1.35 μg/m³, with standard deviations of 0.91 and 0.66, respectively. The authors reported that the airborne concentrations were independent of height from ground level up to 7 m.

PedCo-Environmental[9] measured lead concentrations at heights of 5 and 20 ft at sites near streets in

Kansas City, Mo. and Cincinnati, O. The sampling sites in Kansas City were described as unsheltered, unbiased by localized pollution influences, and not immediately surrounded by large buildings. The Cincinnati study area was located in a primarily residential area with one commercial street. Samplers were operated for 24-hr periods from 8 a.m. to 8 a.m.; but a few 12-hr samples were collected from 8 a.m. to 8 p.m. Data were obtained at Kansas City on 35 days and at Cincinnati on 33 days. The range and average values reported are shown in Table 7-8. In all cases except two, the measured concentrations were higher at 5 ft than at 20 ft. Note that the difference between the east side and west side of the streets was approximately the same as the difference between 5 and 20 ft in height.

TABLE 7-8. AIRBORNE LEAD CONCENTRATIONS AT 5- AND 20-FT ELEVATIONS ABOVE STREET LEVEL[9] ($\mu g/m^3$)

		Averages					
		East side of street			West side of street		
Location	Range	20 ft	5 ft	Diff.	20 ft	5 ft	Diff.
Kansas City	0.8 - 4.0	1.7	2.0	0.3	1.5	1.7	0.2
Cincinnati	0.1 - 4.6	0.9	1.4	0.5	0.6	0.8	0.2

These data reflect the strong influence of the geometry of the boundary layer, wind, and atmospheric stability conditions on the vertical gradient of lead resulting from automobile emissions. The varability of concentration with height is further complicated by elevated emissions (i.e., from stacks). Concentrations measured from sampling stations on the roofs of buildings several stories high may not reflect actual human exposure conditions, but neither would a single sampling station located at ground level in a building complex. The height variation in concentration resulting from vertical diffusion of automobile emissions is likely to be small compared to temporal and spatial variations resulting from surface geometry, wind, and atmospheric conditions.

7.2 MOBILE SOURCE EXPOSURES

Several major studies have been undertaken to determine the lead levels in the air and in settled dust near busy highways that are far from any stationary lead source. Among the most intensive of these studies was the Los Angeles Catalyst Study of 1974-1975, undertaken by EPA to measure the impact of the catalytic converter on air quality near a major traffic lead source.[10] .

Table 7-9 summarizes the 24-hr ambient concentrations of lead observed at two sites (A and C) on opposite sides of a major freeway during the calendar year 1975. In addition to the monthly average concentration at each site, the monthly average cross-freeway difference in concentrations (C-A) and ratio of concentrations (C/A) are shown in the table. Finally, the percentage of hours in the month when winds were from the directional sector that is most favorable to the detection of cross-freeway differences is shown in the righthand column. The favorable wind direction interval is approximately 160° to 290° and was defined on the basis of concentration of carbon monoxide, which is a tracer for mobile-source pollutants.

TABLE 7-9. MONTHLY AVERAGE LEAD CONCENTRATIONS FOR 1975 LOS ANGELES CATALYST STUDY[10]

Month	Site A. $\mu g/m^3$	Site C. $\mu g/m^3$	Difference. C-A	Ratio. C/A	% Favorable wind direction[a]
January	6.0	6.2	0.2	1.03	28.2
February	4.1	4.8	0.5	1.18	35.2
March	3.2	5.2	2.0	1.63	43.3
April	2.8	6.0	3.3	2.14	47.6
May	1.8	7.4	5.6	4.06	65.6
June	1.4	8.1	6.8	5.68	71.2
July	1.9	8.0	6.1	4.27	68.0
August	2.8	8.4	5.7	3.00	61.6
September	3.7	8.5	5.0	2.30	59.5
October	4.2	7.3	3.3	1.74	49.4
November	4.8	6.6	1.7	1.37	31.6

[a] From A to C (S + SW + W winds).

A very strong seasonal effect is observed in the data, with concentrations at Site C exceeding those at Site A by only 3 percent in January, increasing to a maximum difference of over 400 percent in June, and subsequently decreasing during the fall months (no data were collected during the month of December). As expected, there is a strong linear relationship between the occurrence of favorable wind direction and the observed cross-freeway difference in lead concentration. The correlation coefficient between the two variables is 0.96, indicating that almost all of the variation in the cross-freeway concentration of lead may be accounted for by the seasonal variation in the occurrence of favorable wind direction.

In a study conducted in London, England,[11] ambient air levels of organic lead were measured at urban sites. Concentrations of 0.04 to 0.11 μg organic Pb/m^3 were found on streets of varying widths and traffic flow. These values were 0.3 to 2.6 percent of total airborne lead. The level of organic lead inside a busy tunnel was 0.02 $\mu g/m^3$, or 0.1 percent of the total airborne lead. Not surprisingly, organic lead concentrations measured at a busy service station ranged from 0.21 to 0.59 $\mu g/m^3$, or 3.9 to 9.7 percent of total airborne lead at that site. At a less busy service station, the concentration of organic lead was 0.07 $\mu g/m^3$, or 4.2 percent of total airborne lead at that site.

Data obtained in a number of other studies on lead in dusts near roadways are summarized in Tables 7-10 and 7-11. The above data demonstrate that abnormally high concentrations of lead are found in the air and dust near major roadways, and that people who live or work (e.g., traffic policemen, service station and garage attendants) in these areas are exposed to high lead concentrations.

For comparison, Table 7-12 summarizes lead in dusts from nominally residential urban areas. These concentrations have a wider range than those in traffic-oriented dust samples. They are higher in the vicinity of an identified point source such as the El Paso smelter, but the majority of the readings are lower than those of the traffic-oriented samples.

7.3 POINT SOURCE EXPOSURES

Several studies have been undertaken to investigate lead levels in the vicinity of various point sources of lead emission such as smelters or battery plants. By far the most complete and informative studies are

TABLE 7-10. LEAD DUST ON AND NEAR HEAVILY TRAVELED ROADWAYS

Sampling site	Concentration μg Pb/g
Washington, D.C.:	
Busy intersection	12820
Many sites	(4000-8000)[12]
Chicago:	
Near expressway	8600
Philadelphia:	
Near expressway	(3000-8000)[13]
Brooklyn:	
Near expressway	(900-4900)[14]
New York City:	
Near expressway	2000[15]
Detroit:	
Street dust	(966-1213)[16]
Philadelphia:	
Gutter (low exposure)	1507
Gutter (low exposure)	(270-2626)[17]
Gutter (high exposure)	3262
Gutter (high exposure)	(280-8201)[17]
Miscellaneous U.S. Cities:	
Highways and tunnels	(10000-20000)[18]
Netherlands:	
Heavily traveled roads	5000[19]

TABLE 7-11. LEAD CONTENT IN OR ON ROADSIDE SOIL AND GRASS AS A FUNCTION OF DISTANCE FROM TRAFFIC AND GRASS DEPTH IN PROFILE[a]

Site and distance from road, m	Lead content, $\mu g/g$ dry weight			
	Grass	0-5 cm soil depth	5-10 cm soil depth	10-15 cm soil depth
West of U.S. 1, near Plant Industry Station, Beltsville, Md.:				
8	68.2	522	460	416
16	47.5	378	260	104
32	26.3	164	106	69
West of southbound lanes, Washington-Baltimore Parkway, Bladensburg, Md.:				
8	51.3	540	300	96
16	30.0	202	105	60
32	18.5	140	60	38
West of Interstate 29, Platte City, Mo.:				
8	21.3	242	112	95
16	12.5	140	104	66
32	7.5	61	55	60
North of Seymour Road, Cincinnati, O.:				
8	31.3	150	29	11
16	26.0	101	14	8.2
32	7.6	55	10	6.1

[a] Adapted from Lagerwerff and Specht (cited in Reference 20).

TABLE 7-12. LEAD DUST IN RESIDENTIAL AREAS

Sampling site	Concentration, µg Pb/g
Philadelphia:	
Classroom	2000
Playground	3000
Window frames	1750[17]
Boston and New York:	
House dust	(1000-2000)[21]
Brattleboro, Vt.:	
In home	(500-900)[6]
Birmingham, England:	
In home	5000[14]
New York City:	
Middle class residential	(608-742)[15]
El Paso, Texas, Smeltertown dust at:	
0-1 mile	36853 (2800-103750)[22]
1-2 miles	2726 (100-84000)[22]
2-3 miles	2234 (100-29386)[22]
> 4 miles	2151 (200-22700)[22]
Philadelphia:	
Urban industrial	3855 (929-15680)[23]
Residential	614 (293-1030)[23]
Suburban	830 (277-1517)[23]

those carried out by Yankel et al.[24] and Landrigan et al.[25] in the neighborhood of a smelter in Silver Valley, Idaho. Consequently, the data from these studies will be described here in some detail. Other studies carried out in Solano County, Calif.; Omaha, Neb.; El Paso, Tex.; Helena Valley, Mont.; Missouri; Helsinki, Finland; Meza River Valley, Yugoslavia; and Ontario, Canada, are summarized in Appendix C. Their findings are in substantive agreement with those of the Idaho study.

Yankel and von Lindern[24] defined five study areas arranged concentrically around the smelter and two control areas. Area 1 consisted of homes within 1 mile of the smelter; Area 2, 1 to 2-1/2 miles from smelter; Area 3, 2-1/2 to 6 miles; Area 4, 6 to 15 miles; and Area 5, 15 to 20 miles. Environmental samples, including surface soil, house dust, paint, grass, and garden vegetables were collected at the homes in each area, as were blood samples from the resident children aged 1 to 9 years. The mean lead levels found in the ambient air, soil, and house dust all decreased with increasing distance from the smelter. As mentioned in Chapter 12, the blood lead levels of the resident children followed a similar pattern.

Ambient air lead levels were measured by high-volume samplers stationed throughout the Silver Valley. A highly significant relationship between distance from the smelter and ambient air lead concentration was found, and this relationship was used to estimate the ambient air lead level for any location in the study area. The mean annual ambient air lead levels near a smelter for two different years (1974, 1975) are shown graphically in Figure 7-4. Similar results were obtained for the lead content of soil and house dust. As noted in Chapter 12, the children's blood lead levels correlate quite closely with ambient air lead levels, although this result should not be interpreted as suggesting that direct inhalation of lead is the principal exposure mechanism involved. One result of this pivotal study was that some specific emergency measures were taken in

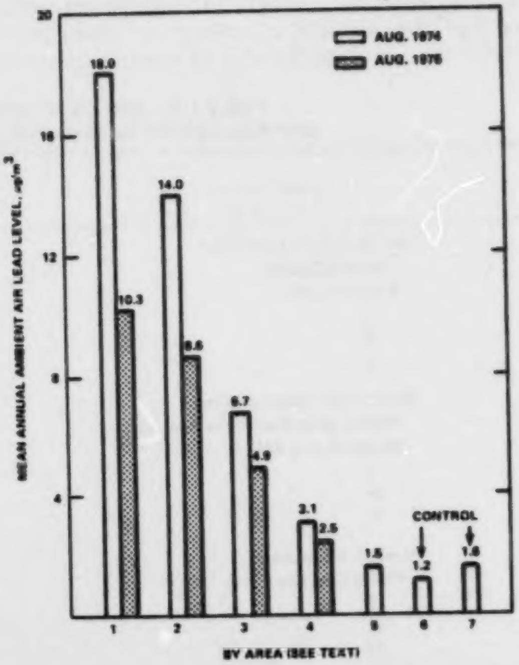

Figure 7-4. Annual ambient air lead concentration near a smelter, by area, before the August 1974 and August 1975 surveys.[24] Area 1 is within 1 mile of smelter; Area 2 is 1 to 1-1/2 miles from smelter; Area 3, 2-1/2 to 6 miles; Area 4, 6 to 15 miles; and Area 5, 15 to 20 miles.

1974 (including covering contaminated soil with clean soil and reducing smelter emissions) and brought about a decrease in blood lead levels that were measured a year later. The details of the blood lead levels and their significance are presented in Chapter 12. The conclusion to be drawn from this study (and from the similar studies referred to above) is that people who live in the vicinity of a major industrial source of lead (e.g., a smelter) are exposed to abnormally high lead concentrations.

7.4 DIETARY EXPOSURES

7.4.1 Food

The route by which most people receive the largest portion of their daily lead intake is through foods, with estimates of the daily dietary lead intake for adult males ranging from 100 to 500 μg/day.[26] Only a fraction of this ingested lead is absorbed, as discussed in Chapter 10.

The sources of the lead content of unprocessed vegetable foods have been noted earlier (Section 6.4.3). Studies of the lead associated with crops (near highways) have shown that both lead taken up from soil and aerosol lead delivered by deposition are found with the edible portions of common vegetable crops. However, there is enormous variability in the amount of lead associated with such crops and in the relative amounts of lead in and on the plants. Several factors are involved, the most prominent of which are: the plant species, the traffic density, the meteorological conditions, and the local soil conditions.[27-33] The variability induced by differences in the above factors, coupled with the fact that many studies have neglected differentiation between lead on plants versus lead in the plants, makes it difficult to generalize. Data of Schuck and Locke[29] suggest that in some cases (e.g., tomatoes and oranges), much of the surface lead is readily removed by washing. But as noted in Section 6.4.3, this is not universally true; in some cases much more vigorous washing procedures are required.

In view of the wide variability of soil conditions (pH, organic matter, cation exchange capacity, phosphorus content, etc.), of meteorology (especially wind conditions and rainfall), and of the effects of species diversity on the routes of lead accumulation, only crude general correlations between air lead levels and food crop lead levels are possible. This is influenced by the fact that the lead associated with plants may be derived from natural sources, from automotive sources, and from other sources such as manufacturing or combustion. One study in Southern California reported that 60 to 70 percent of the lead associated with oat tops was directly attributable to automobile (aerosol) emissions, but it did not distinguish between lead in the edible portion (grain) and lead on the hulls or chaff.[27] This same study reported that lettuce grown in the Salinas Valley had 3 to 25 ppm lead (dry weight) associated with it, whereas the soil lead content was only 10 ppm. The lead content in the lettuce was reported to be 0.15 to 1.5 ppm on a fresh weight basis. The limited data accumulated were used to deduce that the excess lead was delivered to the lettuce by aerial emission from autos, and that removal of lead from automobile exhaust would reduce the lead content of the lettuce by as much as 80 percent.[27] In other areas, the contribution would be smaller. Though these figures may be accurate, they are based on some rather tenuous assumptions that are not well supported by observation and very limited data. The estimates must thus be considered with caution. Moreover, one cannot extrapolate from lettuce or oats to all crops.

The possible connection between air lead and food lead may be underscored by comparisons between leafy vegetables and food grains. Studies have shown that the edible portions of grains absorb very little air lead,[32] whereas the leafy vegetables retain appreciable quantities.[27-29] An FDA survey[34] shows that grains contain approximately 20 percent as much lead as the leafy vegetables. It cannot be concluded, however, that 80 percent of the lead in all leafy vegetables derives directly from air because the difference must also reflect species-dependent differences in uptake from soil.

An overall analysis of the data available supports the contention that plants grown near busy highways consistently have more lead in and on them than those in other areas. This difference is typically very hard to detect at distances greater than about 100 to 200 m from the highway, thereby reflecting the fact that large percentages of the aerosol lead fall out near roadways. It appears reasonable to point out that the vast majority of edible crops marketed in this country are grown at distances of more than 100 to 200 m from the highway and that much of the aerosol lead can be removed from association with the plants by processing. Clearly there are exceptions that will influence both sides of the question. For the present, however, the available data are not sufficient to permit the quantitative estimate of the contribution of automotive lead to foodstuffs on a national or even regional scale.

The concentrations of lead in various food items are highly variable, and as much variation is found within specific food items as between different food categories. Schroeder and Balassa,[35] in a study of American foods, have found that the ranges are 0 to 1.5 mg/kg (ppm) for condiments, 0.2 to 2.5 mg/kg for fish and other seafood, 0 to 3.7 mg/kg for meats and eggs, 0 to 1.39 mg/kg for grains, and 0 to 1.3 mg/kg for vegetables. All of these values refer to unprocessed foods. A British report[36] on lead in foods describes similar ranges for meat and eggs, grain products (flour and bread), and vegetables; but concentrations up to 14 mg/kg were found in condiments, and up to 18 mg/kg in certain shellfish.

The amount of lead taken in with food varies from person to person. It depends on (a) the total amount of food eaten, (b) the history of the food during growth, (c) its opportunity to acquire intrinsic lead (absorbed from soil or water) and extrinsic lead (deposited insecticides or contaminated dusts), and (d) dietary habits (such as using fresh rather than canned foods). On a per-weight basis, the dietary intake of lead by children has been shown to be two or three times that of adults. This additional dietary intake is especially significant when the lead added to food by processing and to water by plumbing *(vide infra)* is considered. A 1974 FDA survey of heavy metals in foods[37] found relatively high lead concentrations in metal-canned foods. In the adult food category, canned foods averaged 0.376 ppm lead, and non-canned foods averaged 0.156 ppm lead. In the baby food category, canned foods (juices) averaged 0.329 ppm lead, and foods in jars averaged 0.090 ppm. The report of the survey concludes that from the age of about 1 year on, canned foods comprise 11 to 12 percent of a person's diet, but they contribute about 30 percent of the average dietary lead intake. In a comparison made in the United Kingdom,[38] lead concentrations in canned foods were found to vary widely with the precise nature of the food, but they averaged about ten times greater than those in fresh foods.

The soldered seam of tin cans is evidently the major source of this additional lead in canned foods, and increasing lead concentrations in samples of a can's contents taken progressively nearer the seam have been found.[39] Similarly, there is a correlation between increasing lead concentrations in canned products and the increasing ratio of the can's seam length to volume. Of 256 metal-canned foods examined, 37 percent contained 200 μg Pb/liter or more; 12 percent contained 400 μg Pb/liter or more. These levels are markedly above the potable water standard of 50 μg Pb/liter (0.05 mg/kg) established by the U.S. Public Health Service.

Canned pet foods have been found to contain 0.9 to 7.0 ppm lead (approximately 900 to 7,000 μg/liter),[40] and 18 products averaged 2.7 ppm (approximately 2700 μg/liter). Apart from the possible toxic effects on pets, the products pose a hazard to persons who may include them in their own diet.

The lead content in milk is of special interest because it is a major component of the diets of infants and young children. The FDA survey[37] found lead concentrations in whole milk ranging from 10 to 70 μg/liter and averaging about 20 μg/liter. In a recent study by Ziegler et al.,[41] seven samples of baby formula and three samples of whole cow's milk were analyzed in duplicate. Mean concentrations of lead were 18 μg/kg (range 15 to 20) in formula and 10 μg/kg (range 7 to 15) in milk (1 μg/kg is approximately 1 μg/liter). Lead concentration in infant fruit juices ranged from 23 to 327 μg/kg; in five varieties of strained fruits, it ranged from 13 to 131 μg/kg; and in seven varieties of strained vegetables, lead concentration was 14 to 73 μg/kg. Tolan and Elton[38] reported 30 μg Pb/liter in fresh milk in Great Britain and 50 μg Pb/liter in canned (evaporated) milk. Michell and Aldous[39] reported a comparable average for fresh whole milk purchased in New York State — 40 μg Pb/liter. But their results for evaporated milk averaged 202 μg Pb/liter and ranged as high as 820 μg Pb/liter.

Hankin et al.[42] suggest an additional food-related source of potential lead exposure, again predominantly affecting children. The colored portions of wrappers from bakery confections, candies, gums, and frozen confections have lead concentrations ranging from 8 to 10,100 ppm. The higher concentrations are attributed to lead-containing inks. No related illnesses were identified, nor was contamination of the food implied; but the eating of foods from such wrappers and the licking or chewing of the wrappers were postulated as one more avenue for an additional increment to total lead exposure.

The presence of high lead concentrations in illicit whiskey (moonshine), which is still popular in some parts of the United States despite the repeal of prohibition, causes lead poisoning in adults. The apparent source of the lead is the soldered joints in the distilling apparatus.

Another potential source of dietary lead poisoning is the use of inadequately glazed earthenware vessels for food storage and cooking. An impressive example of this danger involved the severe poisoning of a physician's family in Idaho and stemmed from drinking orange juice that had been stored in an earthenware pitcher.[43] Similar cases, sometimes including fatalities, have involved other relatively acidic beverages such as fruit juices and soft drinks and have been documented by other workers.[44,45]

Recent reports on lead in European wines[46,47] show concentrations typically averaging from 130 to 190 μg/liter (0.13 to 0.19 ppm) and ranging as high as 299 μg/liter (0.299 ppm). Measurements of lead in domestic wines have not been undertaken; but if the European data are indicative, wines could contain lead concentrations comparable to processed foods previously discussed.

7.4.2 **Water**

The U.S. Public Health Service's standards for drinking water specify that lead should not exceed 50 μg/liter (0.05 ppm). The average adult drinks about 1 liter of water per day. The presence of detectable amounts of lead in untreated public water supplies was shown by Durum[48] to be widespread, but only a few samples contained amounts above the 50 μg/liter standard. Durfor and Becker[49] analyzed untreated and treated water for the largest U.S. cities, and almost all pairs of samples showed a substantial decrease in lead that was ascribable to treatment provided. A maximum lead concentration of 62 μg/liter was detected in finished water from one of several wells used in Salt Lake City to supplement their surface water supply. Some 95 percent of the water supplies sampled, however, had less lead than 10 μg/liter in the treated water before entering the distribution system. Eight of the water supplies distributed water with a pH of less than 7, which could be corrosive to the distribution piping; most of these were in the Northwest. A chemical analysis of 592 interstate carrier water supplies in 1975 showed only 0.3 percent to exceed the 50 μg/liter standard.[50] These samples were collected after treatment but before distribution, and they represent both suspended and dissolved lead. Interstate carrier water supplies serve planes, trains, buses, and vessels in interstate commerce, and they include almost all of the largest U.S. water supplies.

The presence of lead in drinking water may result from contamination of the water source or from the use of lead materials in the water distribution system. Although lead is a relatively minor constituent of the earth's crust, it is widely distributed in low concentrations in sedimentary rock and soils (as discussed in Chapter 3), and naturally occurring deposits may be an important source of contamination in isolated instances. Industrial waste may also contribute to the lead content of water sources, but this appears to be a local and not a widespread problem. The extensive use of lead compounds as gasoline additives has greatly increased the availability of lead for solution in ground and surface waters. For example, in a study in east-central Illinois,[51] the urban portion of an 86-square-mile watershed, which constituted 14 percent of the area, contributed about 75 percent of the lead in the drainage waters. The principal source of this lead is identified as automotive emissions. Detailed data reported for 1 month (June 1972) show that drainage waters from this urban portion contained an average total lead concentration of 69.5 μg/liter, including 6.3 μg/liter of soluble lead. The rural portion yielded an average of lead concentration of 7.4 μg/liter of drainage water, including 2.1 μg/liter of soluble lead.

The major source of lead contamination of drinking water is the water supply system itself. Water that is corrosive can leach considerable amounts of lead from lead plumbing and lead compounds used to join pipe. Several widely adopted codes, such as the ASA-A40 Code, Uniform Plumbing Code, and BOCA Code, allow the use of lead pipe and list lead as an acceptable soldering material for joining pipes that convey water. Lead pipe is currently in use in many parts of the United States for water service lines and interior plumbing, particularly in older urban areas. In a community water supply survey of 969 water systems conducted in nine geographically distributed areas of the United States in 1969 and 1970, it was found that 1.4 percent of all tap water samples exceeded the 50 μg/liter standard.[52] The maximum concentration found was 640 μg/liter total lead. The occurrence of samples exceeding the standard was more prevalent in waters with a relatively low pH and low specific conductance. It was estimated that 2 percent of the survey population of 18.2 million was exposed to high lead levels at the tap.

Hem and Durum[53] discuss the solubility of those species of lead that may be present in drinking water and suggest that the solution of lead from environmental sources may be an important contribution in certain areas, depending on the chemical composition of the runoff water. Above pH 8.0, the solubility of lead is below 10 μg/liter, regardless of the alkalinity of the water. In waters near pH 6.5 with a low alkalinity, however, the solubility of lead could approach or exceed 100 μg/liter. Lazrus et al.[54] determined the lead content of precipitation at 32 points in the United States for a period of 6 months in 1966 and 1967. They reported an average lead concentration of 34 μg/liter after filtering the samples. Samples of rainfall at Menlo Park, Calif., during 1971 showed a wide range of lead concentrations, from a few μg/liter to more than 100 μg/liter.[53] Hem and Durum[53] hypothesize that higher lead concentrations should be anticipated in runoff water and impounded raw water supplies in the Northeast, certain urban areas of the South, and along the Pacific Coast because of low pH and alkalinity in waters. However, in much of the rest of the United States, lead fallout rates and the chemical composition of the runoff (pH >8; alkalinity >100 mg/liter) would minimize the problem. Information to test their hypothesis is limited at present. Of the few surveys of surface waters that have been conducted, most were not done after periods of heavy rainfall, and the surveys that have been done have measured dissolved rather than total lead. Durum[48] measured lead at 700 lake and river sites in the United States. These measurements were primarily single samples taken at times of relatively low stream flows in October and November 1970. Detectable concentrations of dissolved lead (>1 μg/liter) were found in 63 percent of the samples, but only three samples contained more than 50 μg/liter. A large proportion of the samples for the northeastern and southeastern states contained lead above the detection limit, and quite a few of the samples showed levels above 10 μg/liter. This regional distribution of lead in stream water is in accord with the idea that water composition in the eastern states is more commonly favorable for solution of lead. A substantial number of samples from southern California were high in lead, and these influenced the data from the southwestern states. Kopp and Kroner[55] presented data on dissolved lead in rivers and lakes of the United States. The data were gathered over a 5-year period (1962 to 1967) and represent more than 1500 samples. A detectable concentration of dissolved lead was found in 305, or 19.3 percent of the samples; the observed values ranged from 2 to 140 μg/liter. The highest concentration was detected on the Ohio River at Evansville, Indiana. Twenty-seven of their samples exceeded 50 μg/liter. Observed mean observations of >30 μg/liter dissolved lead were found in the following river basins: Ohio, Lake Erie, Upper Mississippi, Missouri, Lower Mississippi, and Colorado.

7.5 OCCUPATIONAL EXPOSURES

The highest and most prolonged exposures to lead are found among workers in the lead smelting, refining, and manufacturing industries.[56] In the work areas, the major route of lead exposure is by inhalation and ingestion of both lead-bearing dusts and fumes. Airborne dusts settle out from the air onto food, water, the workers' clothing, and other objects and are then transferred to the mouth in one fashion or another. Therefore, good housekeeping and, above all, good ventilation have a strong impact on exposure. Exposure levels have been found to be quite high in one factory and quite low in another solely because of differences in ventilation engineering or housekeeping practices and worker education.

7.5.1 Exposures in Lead Mining, Smelting, and Refining

The greatest potential for high-level exposure exists in the process of lead smelting and refining.[56] The most hazardous operations are those in which molten lead and lead alloys are brought to high temperatures, resulting in the vaporization of lead. This is because condensed lead vapor or fume has, to a substantial degree, a small (respirable) particle size range. Thus although the total air lead concentration may be greater in the vicinity of ore-proportioning bins than it is in the vicinity of a blast furnace in a primary smelter, the amount of particle mass in the respirable size range may be much greater near the furnace.

A measure of the potential lead exposure in primary smelters was obtained in a study of three typical installations in Utah.[56] Air lead concentrations near all major operations, as determined using personal monitors worn by the workers, were found to vary from about 100 to more than 4000 μg/m^3. Obviously, the hazard to these workers would be extremely serious were it not for the fact that the use of respirators is mandatory in these particular smelters.

Although there are no comparable data for exposures in secondary smelters, which are found in or near most large cities, the nature of their operation is similar to that of primary smelters except that no ore-processing is involved, since secondary smelters depend on the local supply of lead scrap in the form of discarded electric storage batteries, cable casings, pipes, and other materials for their supply of lead. Consequently, the exposure hazard to workers in secondary smelters is probably similar to that found in the primary smelter study. Hundreds, perhaps thousands, of the small scrap dealers that supply these secondary smelters have their own neighborhood or even backyard melting operations for extracting and reclaiming lead. These operations can contribute substantially to local airborne lead levels.

High levels of atmospheric lead are also found in foundries in which molten lead is alloyed with other metals. Berg and Zenz[57] found in one such operation that average concentrations of lead in various work areas were 280 to 600 μg/m^3. These levels were subsequently reduced to 30 to 40 μg/m^3 with the installation of forced ventilation systems to exhaust the work area atmospheres to the outside.

Exposures for workers involved in lead mining depend to some extent on the solubility of the lead from the ores. The lead sulfide (PbS) in galena is insoluble, and absorption through the lung may be slight. It is not really known how readily absorption takes place. In the stomach, however, some lead sulfide may be converted to slightly soluble lead chloride, which may then be absorbed in moderate amounts.

7.5.2 **Exposures in Welding and Shipbreaking**

When metals that contain lead or are protected with a lead-containing coating (paint or plating) are heated in the process of welding or cutting, copious quantities of lead particles in the respirable size range are emitted into the air. Under conditions of poor ventilation, electric arc welding of zinc silicate-coated steel (determined to contain some 29 mg Pb/in^2 of coating) produced breathing-zone concentrations of lead reaching 15,000 μg/m^3, far in excess of 450 μg/m^3, the current occupational short-term exposure limit (STEL) in the United States.[58] Under good ventilation conditions, a concentration of 140 μg/m^3 was measured.[59]

In a study of salvage workers using oxy-acetylene cutting torches on lead-painted structural steel under conditions of good ventilation, breathing-zone concentrations of lead averaged 1200 μg/m^3 and ranged as high as 2400 μg/m^3.[60]

7.5.3 **Exposures in the Electric Storage Battery Industry**

At all stages in battery manufacture except for final assembly and finishing, workers are exposed to high air lead concentrations, particularly lead oxide dust. Air lead concentrations as high as 5400 μg/m^3 have been recorded in some studies.[56] The hazard in plate casting, which is a molten-metal operation, is from the spillage of dross, resulting in dusty floors. During oxide mixing, which is probably the most hazardous occupation, ventilation is needed when the mix is loaded with lead oxide powder, and frequent cleanup is necessary to prevent the accumulation of dust. In the pasting of the plates, whether by hand or machine, the danger again is from dust which accumulates as the paste dries. Also the forming and stacking processes are dusty, and ventilation is needed there also. The data cited are sufficiently alarming to suggest that respirators must be worn in most of these operations.

7.5.4 **Exposures in the Printing Industry**

In a printing establishment, the exposure to lead is probably in direct proportion to the dispersion of lead oxide dust, secondary to the remelt operation. Brandt and Reichenbach[61] have reported on a 1943 study in which melting pots were located in a variety of places where used type was discarded. The pots were maintained at temperatures ranging from 268° to 446°C. The highest air lead concentration recorded was 570 μg/m^3. Since this report was published, working methods and industrial hygiene conditions have changed considerably; but a marginal degree of hazard still prevails. In 1960, Tsuchiya and Harashima[62] found in several printing shops in Japan lead levels of 30 to 360 μg/m^3 at breathing level.

7.5.5 **Exposures in Alkyl Lead Manufacture**

Workers involved in the manufacture of both tetraethyl lead and tetramethyl lead, two alkyl lead compounds, are exposed to both inorganic and alkyl lead. Some exposure also occurs at the petroleum refineries where the two compounds are blended into gasoline, but no exposure data are available on these blenders.

The major potential hazard in the manufacturing of tetraethyl lead and tetramethyl lead is from skin absorption, but this is guarded against by the use of protective clothing. Linch et al.[63] found a correlation between an index of organic plus inorganic air lead concentrations in a plant and the rate of lead excretion in the urine of the workers. The average concentration of organic lead in the urine was 0.179 mg/m^3 for workers in the tetramethyl lead operation and 0.120 mg/m^3 for workers in the tetraethyl lead operation. The tetramethyl lead reading was probably higher because the reaction between the organic reagent and lead alloy takes place at a somewhat higher temperature and pressure than that employed in tetraethyl lead production.

7.5.6 **Exposures in Other Occupations**

In both the rubber products industry and the plastics industry there are potentially high exposure levels to lead. The potential hazard of the use of lead stearate as a stabilizer in the manufacture of polyvinyl chloride was noted in the 1971 Annual Report of the British Chief Inspector of Factories.[64] The Inspector stated that the number of reported cases of lead poisoning in the plastics industry was second only to that in the lead smelting industry. Scarlato et al.[65] and Maljkovic[66] have reported on other individual cases of exposure. The source of the problem is the dust that is generated when the lead stearate is milled and mixed with the polyvinyl chloride and the plasticizer.

Sakurai et al.[67] in a study of bioindicators of lead exposure, found ambient air concentrations averaging 58 $\mu g/m^3$ in the lead covering department of a rubber hose manufacturing plant. Unfortunately, no ambient air measurements were taken for the other departments or the control group.

7.5.7 Exposures Resulting from Manmade Materials

At least two manmade materials in widespread use are known to contain lead: paint and plastics.

In 1974, the Consumer Product Safety Commission collected selected household paint samples and analyzed them for lead content.[68] Analysis of 489 samples showed that 8 percent of oil-based paints and 1 percent of water-based paints contained greater than 0.5 percent lead (5000 μg Pb/g paint, based on dried solids), which was the statutory limit at the time of the study. The current statutory limit for Federal construction is 0.06 percent. This limit is equivalent to 600 μg Pb/g paint.[68] Old paint that is still on buildings will continue to pose a potential hazard for some time. It can become accessible through flaking, even though painted over with nontoxic paints.

Lead in paint constitutes a potential health problem primarily for children with pica who may habitually ingest 1 to 3 g (or more) of paint per week.[68]

Plastics contain a number of heavy metals that are constituents of organometallic stabilizers added during manufacture. The most commonly used lead-containing stabilizer is dibasic lead stearate, in amounts ranging from 0.5 to 2.0 parts per 100 parts of resin.[69] This stabilizer is normally used in rigid PVC products. Diffusion, or leaching by solvents, is estimated to be quite slow — on the order of 10^{-10} to 10^{-12} cm^2/sec at room temperature — but no definitive information is available.

Incineration of lead-containing plastics may become an increasingly significant source of localized lead pollution. It has been estimated that in the year 2000, for example, there could be approximately 2.54 times 10^9 kg of PVC plastic waste to be disposed of annually, of which about 0.59 times 10^9 kg would probably be incinerated.[70] Assuming that lead will be emitted from the uncontrolled incineration of PVC's at the rate of 0.2 g Pb/kg of waste[71] (a figure applying to all solid waste), about 1.2 times 10^5 kg of lead could be released per year. This would be an increase of more than fourteenfold over the estimate for 1975. Since the greater part of the lead in these incinerated plastic wastes will remain in the ash, electrostatic precipitators can substantially decrease the emitted fraction (to an estimated 0.03 g/kg). But this process only aggravates the difficulties of residual solid waste disposal with its attendant problems of fugitive dust and the potential contamination of soil, surface waters, and groundwaters through leaching from landfill operations.

Lead is present in other products that may constitute sources of lead exposure when used or disposed of. Lead may be found in color newsprint, craft and hobby materials, toothpaste tubes, cosmetic products, candle wicks, pewter and silver hollowware, painted utensils, and decals on glassware. For example, lead in the paint on handles of kitchen utensils has been found by Hankin et al.[72] to range from 0 to 9.7 percent (0 to 97,000 ppm). More than half the paint samples (13 of 21) exceeded the allowable limit for painted toys, which is 0.06 percent.

7.5.8 Historical Changes

Perhaps the most impressive data on the magnitude of environmental contamination by lead and its increase over time are to be found in a small group of recent historical studies that examined levels of the metal in polar snow and ice (Chapter 6). Of particular interest was the 200-fold increase in lead levels over several centuries found by Murozumi et al.[73] in the interior of northern Greenland, and the 10-fold increase through the last century of ice layers reported by Jaworowski[74] in a study of two Polish glaciers. These findings parallel the results of a study by Ruhling and Tyler,[75] which indicated an approximate fourfold increase in lead content in Swedish moss samples taken from the period 1890 to the present. These historical records reflect the increasing distribution of lead caused by man.

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8. EFFECTS OF LEAD ON ECOSYSTEMS

It has been substantiated that lead is a natural constituent of the environment, but natural, background levels of lead in the environment are not known with any degree of certainty. As a natural constituent, lead does not usually pose a threat to the organisms of natural and agroecosystems. However, the widespread use of lead in a variety of chemical forms by man has redistributed the natural lead in the environment and has consequently increased the exposure of the biotic components of ecosystems to unprecedented levels of lead. Concern now exists about the possible threat to these biotic components because of their inherent value to ecosystem stability and because of the ultimate impact that effects of the ecosystem would have on man. Figure 8-1 depicts the environmental flow of lead and the possible exposure routes for plants and animals in the ecosystem.[1]

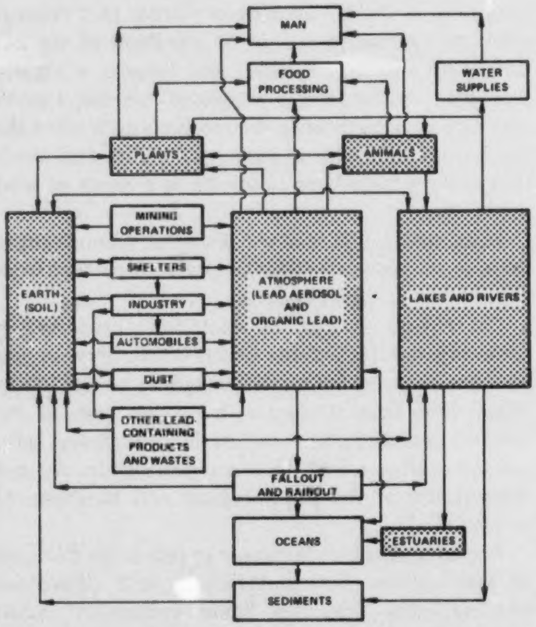

Figure 8-1. Simplified ecologic flow chart for lead showing principal cycling pathways and compartments.[1]

8.1 EFFECTS ON DOMESTIC ANIMALS, WILDLIFE, AND AQUATIC ORGANISMS

8.1.1 Domestic Animals

Lead poisoning, a frequent cause of accidental death in domestic animals for many years,[2] usually results from the ingestion of lead or lead-containing material. Substances that cause lead poisoning include lead-based paints, used motor oil, discarded oil filters, storage batteries, greases, putty, linoleum, and old paint pails. Animals such as cattle, dogs, and cats that have natural licking and chewing habits are particularly susceptible. Horses are not usually poisoned in this manner because they normally do not lick discarded materials. Animals grazing in the vicinity of smelters, mines, and industrial plants from which lead fumes and/or dusts are being emitted or that are fed vegetation harvested from such areas may also be poisoned. The possibility of animals being poisoned from ingestion of roadside pasture contaminated by mobile sources is of concern, but no case of this type has been reported in the literature.[3]

Breathing of lead dusts can be another way whereby animals are exposed to lead, but poisoning of domestic and wild animals as a result of lead inhalation has not been substantiated.

Incidents of lead poisoning in cattle and horses caused by emissions from stationary sources have been reported from Benecia, Calif.;[3] Trail, B.C.;[2] Belleville, Penn.;[4] St. Paul, Minn.;[5] and southeastern Missouri.[6] Deaths from lead poisoning of lambs and sheep in Britain[7] and of horses, sheep, and goats in continental Europe have been reported.[8-11]

Hammond and Aronson[5] have estimated that the minimal cumulative lethal dose of lead for a cow is 6 to 7 mg/kg of body weight per day. They state that this intake represents a concentration of about 300 ppm in the total diet. In cattle that consumed lead-contaminated hay and corn silage grown in a field adjacent to a smelter, fatal lead poisoning occurred after approximately 2 months. In another study,[12] cattle were fed lead at the rate of 5 to 6 mg/kg per day for a period of 2 years without the appearance of visible clinical symptoms. A steer fed the same diet for 33 months, however, showed clinical symptoms of lead poisoning culminating in death.[13] The length of time required for the appearance of overt clinical symptoms of lead poisoning is in most instances directly related to the amount consumed per unit of time.

Horses are more susceptible than cattle to poisoning from the chronic intake of lead. In the Trail, B.C., study,[2] horses grazing near a lead smelter developed overt symptoms of lead poisoning, but cows in the same pasture were not clinically affected. The minimal toxic dosage for a horse has been estimated to be between 1.7 and 2.4 mg/kg body weight daily,[1] which is approximately 80 ppm dry weight in forage.

The reasons for the greater susceptibility of horses are complex. An early symptom of lead poisoning in the horse is paralysis of the nerves of the pharynx and larynx. This interferes with breathing, especially on exercise, and causes the animal to breathe stertorously, or to roar. When severe, this paralysis can produce suffocation and death. In addition, the faulty action of the epiglottis (which closes off the lung during inhalation) permits inhalation of food, which can result in suffocation and death or in severe pneumonia, which can also be fatal.

Colts pastured near the Trail, B.C., smelter[2] showed loss of weight, generalized muscular weakness, stiffness of joints, and harsh, dry coats. Distortion of the limbs occurred, the joints became greatly enlarged and the hocks touched. The laryngeal paralysis usually associated with lead poisoning did not occur. Hupka[9] noted the same symptoms in colts that had grazed on pasture contaminated with flue dust from a metal works. Autopsy showed that the auricular cartilages were detached and loose in the joint. Also noted was an acute catarrhal pneumonia of both lobes of the lungs, with food particles in the bronchi. Roaring typical of chronic lead poisoning did not occur until quite late.

The clinical picture described above has come under close scrutiny in various laboratory studies.[14,15] because of the lack of consensus as to whether it was the result of lead poisoning. Lead and zinc coexist in many ores, and both were present in the two situations referred to above. Under these conditions animals being reared in the area would be exposed to both elements simultaneously. Studies by Willoughby et al.[14] indicated that lameness, blindness, swelling at the epiphyseal ends of long bones, or an increase in the amount of joint fluid in foals resulted from the intake of zinc by itself and zinc and lead together, but not from lead alone. Gunther,[15] in studies based on experimental exposure of colts, reached similar conclusions.

Horses sometimes, though infrequently, pull up plants and eat roots and soil along with leaves. This practice may be a factor in increasing their lead intake[16] relative to that of cattle grazing the same pasture.

Lead poisoning in all domestic animals produces various degrees of derangement of the central nervous system, gastrointestinal tract, muscular system, and hematopoietic system. Younger animals appear to be more sensitive than older ones.[13] Calves may suddenly begin to bellow and stagger about rolling their eyes, frothing at the mouth, and crashing blindly into objects. This phase may last up to 2 hr, after which a sudden collapse occurs. In less severe cases, depression, anorexia, and colic may be observed. The animals may become blind and may grind their teeth, move in a circle, push against objects, and lose their muscle coordination. Mature cattle display fewer overt symptoms, although the syndrome of maniacal excitement is not uncommon.[1]

Clinical symptoms in sheep consist mainly of depression, anorexia, abdominal pain, and diarrhea. Anemia is also commonly associated with lead poisoning in sheep.[1] Pavlicevic[11] notes that clinical symptoms in lambs consist of paralysis of the extremities, pharynx, tongue, and larynx; a rigidly held neck; and an anemic mucous membrane. Lambs may be poisoned through the mother's milk when the ewe is on contaminated pasture. Sterility and abortion in ewes have been observed as a result of lead ingestion.[1]

Toxic dosages of lead for domestic animals other than horses and cattle have not been calculated from statistically reliable studies.

The effects of lead on biological processes in animals generally include effects on the nervous and hematopoietic systems and the kidney tissue. These effects have been studied with various types of test animals (primarily the rat) at the enzymatic, subcellular, cellular, and tissue morphology levels; and systemically at the physiological and biochemical levels.

The most sensitive indicator in rats is the decrease of the enzyme δ-aminolevulinic acid dehydrase (ALAD) that regulates heme synthesis.[17] Lead clearly affects test animals at the subcellular and enzymatic levels of biological function.

8.1.2 Wildlife

Lead has so permeated the environment that it is now known to be a regularly occurring constituent of all animal life. Birds and other wild animals are exposed to a wide range of lead levels. Measurable amounts of lead may be found in the tissues of these animals, and lead poisonings have occurred.

Toxic effects from the ingestion of spent lead shot were first observed in ducks in 1919 and have since been recognized as a major health problem in both aquatic and upland species of waterfowl. It has been estimated that thousands of ducks, geese, and swans die of lead poisoning each year.[18] Lead poisoning from spent shot has also been reported in game birds such as wild pheasants, mourning doves, and quail.[19] The scope of the problem becomes readily apparent when it is noted that the majority of the birds die after the hunting season is over; thus it is the breeding stock that is lost. Spent shotgun pellets have been removed from the gizzards of birds with lead poisoning.[20]

Pieces of lead metal when swallowed are normally not harmful to humans or other mammals because they pass through the digestive tract too rapidly to lose more than a minor portion of their surfaces to digestive enzymes and other substances. But it should be noted that persons who consistently eat game often have somewhat elevated blood lead levels and high fecal lead levels from swallowing lead pellets. The gizzard of a bird, however, is a comminuting organ for food that operates by grinding up the food in a muscular sack containing small stones that the bird has swallowed. Spent shotgun pellets lying in the sediment on the bottoms of lakes are picked up by the bottom-feeding ducks in the same manner as pebbles. Because the shot are soft, they are ground fine and made quite susceptible to digestive action rather than just coming into superficial contact with the digestive tract, as in most other animals.[21] Lead released from the gizzard is absorbed by the lower digestive tract. One number-6 lead shot can furnish enough lead to induce fatal lead poisoning in a duck; but, the length of time a pellet is retained in the gizzard depends partly on its size and partly on the fiber content of the diet. A high fiber diet is especially conducive to lead poisoning. The number of shot required to poison a bird also depends on the size of the bird itself. Six number-6 shot are always fatal for mallards, and four or five number-4 shot are generally fatal for Canadian geese.[22]

The symptoms generally associated with lead poisoning in waterfowl are lethargy, anorexia, weakness, flaccid paralysis, emaciation, anemia, greenish diarrhea, impaction of the proventriculus, and distention of the gall bladder.[22] Waterfowl appear to be at least twice as sensitive to the biochemical effects of lead as are man and other mammals.[23] Death appears to be associated with the inhibition of δ-aminolevulinic acid dehydrase (ALAD) by lead.[23,24] In instances where insufficient lead is ingested to cause death, sterility may result.[1]

In an attempt to prevent the deaths of waterfowl through the ingestion of lead shot, the U.S. Fish and Wildlife Service ordered the use of steel shot during the 1976 hunting season in certain areas of the states in the Atlantic Flyway. Despite strong opposition from the National Rifle Association and hunters, the plan is to extend this limitation to the Mississippi Flyway during 1977.[25]

Waterfowl mortality caused by the toxic effects of lead mine wastes coupled with environmental stress was reported by Chupp and Dalke[26] for the Coeur d'Alene River Valley of Idaho. Because of their feeding habits, feeding waterfowl consumed lead from the sediments in the shallow areas of the river along with metallic materials adhering to roots and tubers of aquatic plants. Ingestion of plants containing lead can also contribute to lead poisoning in waterfowl.

The puffin *(Fratercula arctica)*, a sea bird, is in serious decline. In studies to determine the cause, Parslow et al.[27] note the fact that puffins tend to concentrate lead through the food chain (Table 8-1). The authors were not able, however, to associate observed lead concentrations with the decline of the species.

TABLE 8-1. ACCUMULATION OF CERTAIN HEAVY METALS FROM SEAWATER BY FISH *(Ammodytes* AND *Clupea)* AND A PUFFIN[27]

	Metal levels, ppm, wet weight			Approximate accumulation factors		
Metal	Seawater	Fish	Puffin	Fish/seawater	Puffin/fish	Puffin/seawater
Mercury	0.00003	0.037	0.79	1,230	21	26,300
Lead	0.00003	<0.002	0.36	<67	>180	12,000
Cadmium	0.00011	0.309	1.67	2,800	5.4	15,000
Copper	0.003	1.74	4.49	580	2.6	1,500
Zinc	0.01	53	95	5,300	1.8	9,500

Measurements of lead levels in pigeons[28,29] and in song birds[30] indicate that urban birds have higher lead levels than rural birds (Table 8-2). Bagley and Locke[19] analyzed 28 species of birds and noted the concentration of lead in the livers and bone tissue. Lead in the livers was an indication of acute exposure, and in the bone, of chronic exposure. Liver levels ranged from 0.3 to 5.0 ppm, and bone levels ranged from 0.2 to 26.0 ppm. As might be expected, the highest levels were found in aquatic waterfowl; however, the osprey *(Pandion haliaetus)*, a predator, also showed high bone levels. The bone lead levels are an indication of continued exposure to lead and serve as an indication of normal levels rather than adverse exposure.[19]

TABLE 8-2. SUMMARY OF LEAD CONCENTRATIONS IN BIRD ORGANS AND TISSUES FROM AREAS OF HIGH-LEAD AND LOW-LEAD ENVIRONMENTS
(ppm, dry weight)

Species and lead level[a]	Feathers	Gut	Liver	Lung	Kidney	Bone[b]	Muscle[c]
Red-winged blackbird:							
Low(10)	26.5	2.1[d]	5.8	0.4	2.1[d]	6.9	0.8[d]
High(4)	66.8	2.6[d]	1.2	4.1	4.1[d]	9.1	0.6[d]
House sparrow:							
Low(16)	27.0	2.3	0.6	0.9	3.5	16.9	0.9
High(11)	158.3	26.2	12.0	6.9	33.9	130.4	2.1
Starling:							
Low(11)	6.4	1.3	4.0	2.8[d]	3.6	12.8	0.8[d]
High(13)	225.1	6.0	16.1	5.2[d]	98.5	213.0	2.4[d]
Grackle:							
Low(10)	36.0	1.4	2.5	2.3[d]	3.5	21.5	0.8
High(11)	81.4	10.2	12.1	2.7[d]	13.5	62.8	1.4
Robin:							
Low(10)	25.3	3.2	2.4	2.2	7.3	41.3	1.0[d]
High(10)	79.7	24.5	10.5	10.3	25.0	133.7	1.2[d]

[a] High-lead and low-lead environments are urban and rural areas respectively; high-lead area for red-winged blackbirds is 10 m from an interstate highway. Sample size in parentheses.

[b] Femur.

[c] Pectoral.

[d] Differences between low- and high-lead environments not significant at the 0.05 level; all others significant at least at the 0.05 level.

Studies of lead exposure and effects in wild animals other than birds are infrequent. Braham[31] studied the distribution and concentration in the California sea lion *(Zalophus californianus)*. He noted that accumulation was occurring in the species but could detect no adverse effects at the time of the study. The exposure of small mammals and selected invertebrates near roadways has also been studied.[32-38] In general, gradients in body lead concentrations declined with increasing distance from the road. The body lead gradients usually were similar in pattern to, though lower than, the soil level gradients; but interesting exceptions were observed in some cases. No evidence of toxicity was observed in any of these animals individually or in relation to population distributions.

An analysis of lead concentrations in 3 species of small mammals from 11 sites in Huntingdonshire, Great Britian,[32] showed that the lead concentrations in the animals were more closely associated with the type of food consumed than with nearness to the highway where the air lead concentrations were highest.

One hundred and one mammals — 51 long-tailed field mice *(Apodemus sylvalicus)*, 27 bank voles *(Clethrionomys glariolus)*, and 23 field moles *(Microtus agrestis)* — were trapped along roadsides.[32] The concentration of lead was significantly higher in *Microtus* than in *Clethrionomys* or *Apodemus* (Figure 8-2). The marked differences among the lead concentrations of the three species can be accounted for by species behavior and food consumed. *Microtus* eats grass as its staple food, whereas *Apodemus* feeds on grain, seedlings, buds, fruit, hazel nuts, and animals such as snails and insects. The range of food for *Clethrionomys* encompasses that of both the other species, but the habitat is restricted to hedges rather than the open field *(Apodemus)* or the roadside *(Microtus)*. Differences in food and food contamination may therefore account for the differences in lead concentrations in the three species.

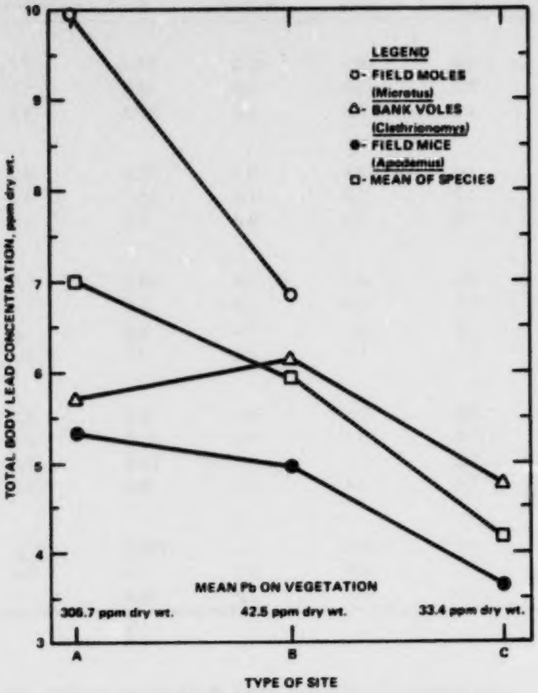

Figure 8-2. Concentration of lead in three species of small mammals trapped beside major and minor roads and at arable and woodland sites.[33]

In a study in central Illinois, samples of small mammals were obtained from a range of environments including those within 10 m of a high-traffic-volume road (> 12,000 vehicles/24hr), those within 5 m of medium-use roads (2000 to 6000 vehicles/24 hr), those within 5 m of low-use roads (< 2000 vehicles/24 hr), and those in urban areas (approximately 100,000 inhabitants).[38]

All species except the white-footed mouse *(Peromyscus leucopus)*, showed higher concentrations of lead in habitats adjacent to high-traffic-volume situations, especially in urban areas. Since the home range of this species averages more than 50 m in diameter, even those individuals caught nearest the highway were undoubtedly spending considerable time much further removed from the traffic source, possibly accounting for the low lead levels in these animals.

There was also a correlation between habitat requirements and lead concentrations in small mammals captured near high-traffic roadways. Species requiring dense vegetation — the prairie vole *(Microtus ochrogaster)*, the short-tailed shrew *(Blarina brevicauda)*, the least shrew *(Cryptotis parva)*, and the white harvest mouse *(Reithrodontomys megalotis)* — had higher total body lead burdens and higher levels in selected tissues than did those species such as the white-footed mouse *(Peromyscus maniculatus)* and the house mouse *(Mus musculus)* that extend their home ranges into cultivated fields. There was also a correlation between feeding habits and lead concentrations in body tissues. Insectivores (the shrews) had the highest lead concentrations; herbivores (voles) had intermediate concentrations; and granivores (deer mice, white-footed mice, and house mice) had the lowest concentrations, reflecting the fact that lead concentrations in seed tissue are usually extremely low (< 1 ppm).

It is highly doubtful that the very low concentrations of lead in these mammals (Table 8-3) could be having a significant impact on their population dynamics.

Studies of lead concentrations in insects in central Illinois ecosystems have shown positive correlations with lead emission levels, decreasing from areas adjacent to heavily traveled roads to areas remote from roads (Table 8-4).[39] There was also a strong trend of increasing lead content from sucking to chewing to predatory insects collected near high-traffic roadways (Figure 8-3). Chewing insects probably ingested more lead from deposits on leaves than did insects that suck liquids from the internal vascular tissues of plants. Data on predatory insects that feed on lead-containing herbivores suggest that lead is selectively retained in the body, leading to biological concentration in this two-trophic (feeding-level) system.[39]

Definitive studies correlating toxicity with environmental lead concentration have not been done.

8.1.3 Aquatic Organisms

Acute lead toxicity in aquatic organisms has been observed and studied experimentally. Lead toxicity in fish is partially related to drainage from metallic wastes into streams. Early experiments were carried out in England where contamination of natural waters by lead mining caused the disappearance of fish from streams.[1] Although the effect of lead on lower forms of life is not well documented, it appears to be less toxic than in higher forms.[1,40]

Apparently, lead and other metals are irritating to the skin of many freshwater fish and cause an unusual reaction. The presence of metal in the water around them causes a copious secretion of mucus over the whole body surface, particularly in the gill

TABLE 8-3. MEAN LEAD CONCENTRATIONS IN ORGANS AND TISSUES OF SMALL MAMMALS FROM INDICATED AREAS OF ENVIRONMENTAL LEAD EXPOSURE[38]
(ppm, dry weight)

Species and exposure area	Total body	Gut	Spleen	Liver	Lung	Kidney	Bone[a]	Muscle[b]
Blarina brevicauda:								
High	18.4	24.0	4.5	4.6	16.9	12.4	67.1	9.7
Medium	6.7	7.0	3.6	2.0	5.6	5.8	19.9	5.7
Low	5.7	3.1	2.3	1.0	7.8	3.9	12.2	5.4
Microtus ochrogaster:								
High	5.1	11.0	5.3	1.6	2.8	8.1	16.6	8.2
Medium	5.9	18.4	2.2	1.2	1.8	7.6	23.2	3.0
Low	1.9	2.8	2.4	1.0	1.3	2.8	4.6	2.0
Peromyscus maniculatus:								
High	6.3	19.2	19.4	3.5	6.4	7.9	24.6	6.8
Medium	4.3	6.0	3.0	1.7	2.4	9.0	8.0	7.4
Low	3.3	4.5	6.5	1.8	6.1	3.0	6.4	1.8
Control[c]	3.1	4.3	3.7	1.1	1.5	1.8	5.7	2.1
Mus musculus:								
High	6.8	18.6	12.1	2.9	2.8	8.1	19.2	5.9
Medium	6.0	8.8	3.1	1.6	3.4	6.6	21.0	3.9
Low	6.7	4.8	5.1	1.6	1.7	3.1	23.5	3.4
Control[c]	2.0	2.7	2.1	1.9	3.4	3.4	9.3	3.8
Reithrodontomys megalotis:								
High	12.3	17.8	145	4.7	20.9	—	109.5	27.5
Medium	3.0	6.2	9.2	1.1	4.2	2.1	—	4.4
Low	2.7±	3.5	5.6	2.3	4.7	4.8	18.4	—

[a] Femur.
[b] Thigh.
[c] Control areas are fields more than 50 m from a road.

TABLE 8-4. LEAD CONCENTRATIONS OF INSECTS AT TWO DISTANCES FROM A HIGH-TRAFFIC-VOLUME ROAD (INTERSTATE HIGHWAY)[39]
(ppm)

Feeding type	Distance	
	0 to 7 m from pavement	13 to 20 m from pavement
Sucking	15.7	9.8
Chewing	27.3	10.4
Predatory	31.0	20.0
Mean	24.7	13.4

area. Analysis of this mucus has revealed the presence of "considerable quantitities" of lead.[41] The mucus does not, however, prevent absorption of lead into the fish. If the metal level is low, the process is harmless because the excreted film is readily shed; but if higher levels are present, the mucus blanket generated may suffocate the animal before it can be shed. The phenomenon has been observed only in freshwater fish and is subject to modification by water hardness, temperature, and other factors. It should be emphasized that the process described above is entirely external and unrelated to lead levels in the body of the fish. In some cases of lead poisoning in freshwater fish, mucus formation has not been observed.

Symptoms of chronic lead poisoning in fish include anemia, functional damage to the inner organs, possible damage to the respiratory system, growth inhibition, and retardation of sexual maturity.[1,42]

A study in central Illinois[43] of both urban and rural tributaries of the Saline Branch of the Vermilion River showed that lead appears to be taken up by aquatic organisms by means of external contact rather than by ingestion. Lead concentrations in aquatic organisms were found to be related to the amount of contact with substrates, such as sediments (Figure 8-4), that contain the highest lead concentrations in the streams. Thus species differences in concentrations are determined in part by habitat preference and feeding habits.

Filtered water from the two streams had concentrations of lead varying from 0 to 15 mg/liter of water (ppm), and suspended solids in the water contained 15 to 200 ppm lead. The highest levels occurred in the urban stream. The upper 10 cm of sediments in the urban stream contained an average lead concentration of 387.5 ppm, more than 10 times greater than that in the rural stream. Fish in the rural stream contained an average of 1.4 to 4.1 ppm

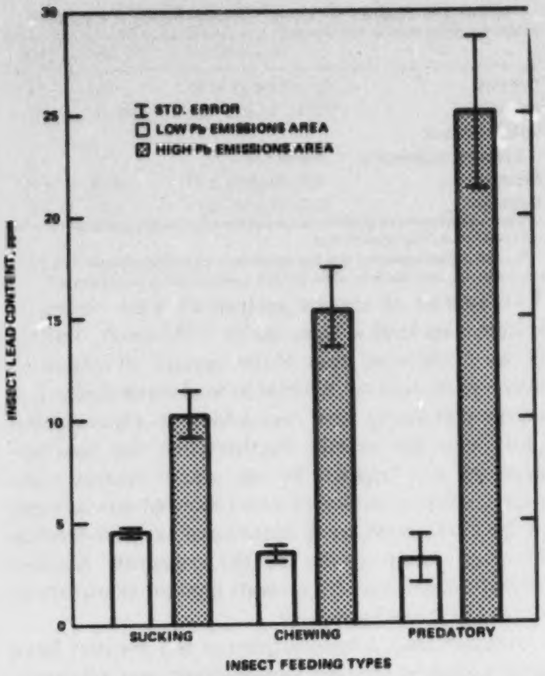

Figure 8-3. Mean lead content in grouped insect samples taken from low- and high-lead-emission areas for sucking, chewing, and predatory feeding types.[39]

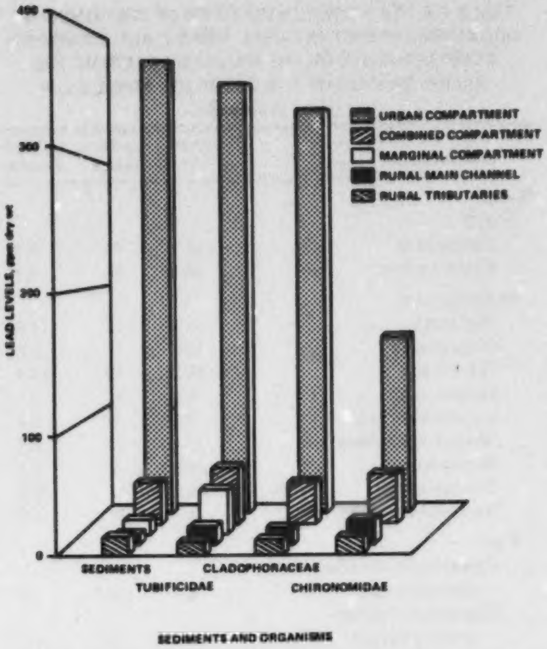

Figure 8-4. Mean lead levels in representative organisms and sediments of the compartments of the drainage basin of the Saline Branch of the Vermilion River, Ill.[43]

of lead in dry tissue (Table 8-5).[43] No fish were found in the urban stream. Lead levels in the invertebrates ranged from about 5 to 20 ppm in the rural stream to more than 350 ppm in the urban stream. These data appear to be in agreement with relative lead levels found in tubificid worms, clams, and fish in the Illinois River.[40]

Hardisty et al.[44] studied lead levels in estuarine fish, but were unable to determine any biological effects of lead. Merlini and Pozzi[45] studied lead accumulation by freshwater fish. Ionic lead (as Pb^{++}) was concentrated threefold when the pH of the lake water was lowered. Lead toxicity in fish was not reported.

Toxicity varies with pH, temperature, hardness, and other water properties.[40] The concentrations of lead injurious to fish and other aquatic and marine life may be found in *Water Quality Criteria, 1972.*[46] The 96-hr LC_{50} value in soft water for rainbow trout *(Salmo gairdneri)* has been reported to be 1 mg/liter. Pickering and Henderson[47] list the soft water LC_{50} values for fathead minnows *(Pimephales promelas)* and bluegills *(Lepomis macrochirus)* as being 5 to 7, and 23.8 mg/liter, respectively. In hard water, the LC_{50} values for the last two species are reported as being 482 and 442 mg/liter, respectively;[47] whereas for rainbow trout, Davies and Everhard[42] report 471 mg/liter. Detrimental effects on fish species occur at concentrations as low as 0.1 mg/liter. In studies of rainbow trout, mortalities attributed to lead occurred at the high test concentrations, which in soft water were 95.2 μg Pb/liter and in hard water, 3.24 mg/liter total lead or 0.064 mg/liter free lead.[42] Physical abnormalities occurred between 11.9 and 6.0 μg Pb/liter in soft water and between 0.12 and 0.36 mg/liter total lead (0.018 and 0.032 mg/liter free lead) in hard water. In *Daphnia magna,* an effect on reproduction has been observed at 0.03 mg Pb/liter.[48]

A study of long-term effects of lead exposure on three generations of brook trout *(Salvelinus fontinalis)* indicated that all second generation trout exposed to 235 and 474 μg Pb/liter developed severe spinal deformities (scoliosis), and 34 percent of those exposed to 119 μg Pb/liter developed scoliosis. Of the newly hatched third generation alevins exposed to 119 μg Pb/liter, 21 percent developed scoliosis. Analysis of residues in eggs, alevins, and juveniles indicated that accumulation of lead occurred during these life stages.[49]

Weir and Hine[50] utilized a conditioned avoidance

TABLE 8-5. LEAD CONCENTRATIONS OF PREDOMINANT ORGANISMS FROM THE RURAL, URBAN, AND COMBINED COMPARTMENTS OF THE DRAINAGE BASIN OF THE SALINE BRANCH OF THE VERMILION RIVER, ILL.[48]
(ppm, dry weight)

Compartment and organism	Arithmetic mean	Number of samples	Standard deviation
Rural:			
Plants:			
Cladophora	20.1	11	5.1
Potamogeton	30.0	15	5.4
Invertebrates:			
Hirudinea	12.6	12	14.8
Oligochaeta	13.2	7	7.6
Tubificidae	16.0	13	11.8
Sphaeriidae	5.5	11	3.1
Lirceus fontinalis	7.6	5	3.4
Hexagenia limbata	10.4	15	9.7
Anisoptera	6.6	6	2.4
Chironomidae	20.1	12	18.2
Decapoda	4.7	23	5.2
Fish:			
Catostomus commersoni (white sucker)	2.4	19	1.6
Etheostoma nigrum (Johnny darter)	4.1	9	2.4
Ericymba buccata (Silverjaw minnow)	1.8	29	0.9
Notropis umbratilus (Redfin shiner)	1.9	29	0.6
Pimephales notatus (Bluntnose minnow)	2.7	63	2.7
Semotilus atromaculatus (Creek chub)	1.4	35	0.6
Urban:			
Plants:			
Cladophora	347	6	139
Invertebrates:			
Tubificidae	367	29	373
Chironomidae	153	5	106
Decapoda	11	4	
Combined:			
Plants:			
Elodea	89.9	22	93.3
Cladophora	34.9	7	7.5
Invertebrates:			
Tubificidae	48.6	71	33.9
Chironomidae	42.7	12	16.4
Physa	41.7	10	25.5
Psychodidae	32.3	4	25.5

technique to assess the deleterious effects of four metal ions, including lead, on goldfish. Behavioral impairment was noted following sublethal concentrations of lead nitrate (Table 8-6). The lowest concentration that gave significant impairment was 0,07 ppm.

Shellfish have been reported to concentrate lead.[1] Two species of marine gastropods were shown to concentrate lead in their shells.[51] However, Valiela et al.[52] reported that three species of estuarine bivalves showed no increase in lead when sludge fertilizer containing lead was added to experimental plots in a salt marsh. Furthermore, the lead apparently was trapped by the marsh surface sediments, since no increases were recorded downstream in the detritus on creek bottoms or in filter-feeding bivalves. Lead uptake by the cordgrass *Spartina alterniflora* reduces by a small amount the quantity of lead in the sediments.[53]

TABLE 8-6. SUMMARY OF GOLDFISH TOXICITY DATA[50]

Ion	LC_{50}, ppm[a,b]	LC_1, ppm[b]	Slope
Arsenic	32.0 (41.6 to 24.6)	1.5	1.4
Lead	110.0 (121.0 to 100.0)	60.0	1.2
Lead (without calcium carbonate)	6.6 (9.2 to 4.7)	1.5	1.6
Mercury	0.82 (0.90 to 0.75)	0.36	1.2
Selenium	12.0 (17.0 to 7.9)	1.0	2.5

[a] Based on a 7-day survival time.

[b] Lowest concentrations of ions that significantly impaired conditioned avoidance responses and their fractions of the 50- and 1-percent lethal concentrations.

Aquatic lead concentrations of 0.5 mg/liter have been shown to be toxic to flagellates and infusoria, the microscopic animals that frequently develop in decaying organic matter. Bacterial decomposition of organic matter is inhibited by lead concentrations of 0.1 to 0.5 mg/liter.[54]

8.2 EFFECTS ON PLANTS

8.2.1 Routes of Plant Exposures

Plants may be exposed to lead through the leaves, stems, bark, or roots. The extent of exposure depends on the amount of lead in the immediate environment and the form and availability of that lead.

8.2.1.1 LEAVES, STEMS, AND BARK

Particulate substances in the air, including lead, are deposited on plant surfaces by fallout, impaction, and precipitation.[55] Precipitation may, in addition to depositing material, wash off or leach out material from the plant surface or tissue. Wind and sloughing of the cuticle wax may also remove deposited material. Thus, meteorological factors are important in determining the fate of compounds that come into contact with plant surfaces. The morphology of the plant surface, however, plays the major role in determining the type and quantity of material that will be retained by that plant surface.[56,57] Epidermal cells of the aerial parts of plants are usually coated with a waxy substance, cutin, and often form unicellular or multicellular hairs, spines, or glands. In addition, secretions from glandular hairs may make leaf surfaces sticky; thus, particulate material can accumulate on the plant surface, particularly the leaves. However, particulate matter must enter the internal plant tissues to affect the plant.[56] Franke[58] suggests that the cutin is penetrable via intermolecular spaces and that cuticle has been shown to be permeable to both organic and inorganic ions and to undissociated molecules. The capability of an ion to penetrate is determined by its charge, adsorbability, and radius.

Vascular plants have small surface openings, called stomata and lenticels, that function in gas exchange. Stomata are also sites of exchange of aqueous substances under certain conditions.[58] Stomata occur in the epidermis of leaves and young stems. Lenticels are found on older stems of woody species. Surrounding the stomatal pores are guard cells that open and close the pores through changes in their turgidity. Gas exchange, which takes place through the stomata as the result of a concentration gradient, is a passive phenomenon unlike the active breathing of animals.

Large deposits of inert, insoluble metal compounds on the leaves are probably of little consequence to a plant. The most important factor in determining foliar penetration is the solubility of the individual metal.[56,58] The insolubility of lead is undoubtedly a major reason that little incorporation and accumulation occur through the leaf surface.[56]

Carlson et al.[57] experimentally fumigated soybean *(Glycine max* L.) with $PbCl_2$ aerosol particulate; no intraplant movement was noted. Simulated rainfall removed up to 95 percent of the topically applied lead. Studies by Arvik and Zimdahl[59,60] indicated that only extremely small amounts of lead could penetrate plant cuticles, even after extended exposure. Increased penetration of some cuticles occurred after the removal of waxes, but penetration seemed more related to plant species than to cuticle thickness. Oats *(Avena sativa* L.) and lettuce (*Lactuca sativa* var. Black-Seeded Simpson) are two species, according to Rabinowitz, whose leaves atmospheric lead is capable of penetrating.[61] The only conclusion possible from current data is that airborne lead can be taken up by the foliage of some plants, but only in extremely small amounts.

A recent report[62] suggests that grasses and small herbaceous plants in the field, as well as pea plants (*Pisum sativum* L.) and pine tree seedlings (*Pinus sylvestris* L.) in the laboratory, when grown in nutrient solution, release lead and zinc into the air. It is questionable whether the lead exuded from plant leaves adds appreciably to the atmospheric burden. The complexities of lead movement from soil into plants make it unlikely that plants are capable of exuding large amounts into the air.

Particles containing lead, in addition to chlorine and bromine, have been found embedded in the bark of both pine and elm trees growing near highways. The lead content of the particles on the trees decreased over a 3-year period, and the particles on the bark of elm trees showed less lead than those on pine trees.[63] No evidence exists to show that lead entered the trees through the bark.

Trees have been used as indicators of increasing environmental lead concentrations with time.[64] Studies in central Illinois have shown a fivefold increase in lead in tree rings during the last 50 years (Figure 8-5). This graphically illustrates the increase in environmental lead uptake that has occurred in that time. However, data reported by Holtzman on four hardwood trees in a rural suburban area and on one tree in a suburban area near Chicago (tree ages were 100 to 120 years) showed no consistent increase or decrease in lead in the tree rings.[65]

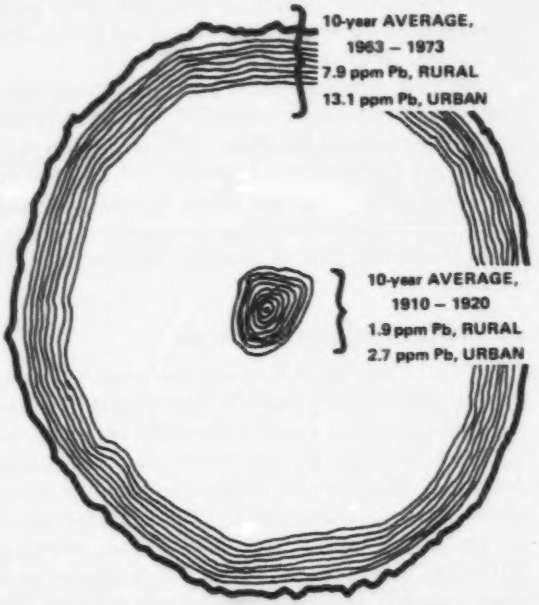

Figure 8-5. Tree ring analysis of lead concentrations in urban and rural trees.[63]

8.2.1.2 ROOTS

The root system is the major pathway of plant exposure to lead, as lead in the soil may be absorbed by the roots and moved into the plant.[60,66-77] But the total lead content of the soil is only one of several interacting factors determining plant uptake. These factors are not well understood, but uptake is known to be influenced by plant species and by the available lead pool in soils.[66,71-74] The pool of available lead is determined by soil pH, soil organic and clay fractions, and the cation exchange capacity as well as other soil sorption characteristics.[66,70-81] Absorption of lead by plant roots is inversely related to cation exchange capacity.[74,79,80] The total lead in the soil in relation to cation exchange capacity determines lead availability.[80] Roots take up minerals that are in the soil solution;[60,82] thus lead movement into roots is in the form of ions from the soil solution or from weak sorption sites.[60,66,74]

Baumhardt and Welch[70] have shown that the percentage of soluble lead in soil decreases with time as sorption occurs. Soil phosphate[60,75,77,78] and liming,[60,75,83,84] as well as cadmium[85] in soil, reduce the uptake of lead by plant roots. Olson and Skogerboe[86] have identified the primary lead species in their soil tests as lead sulfate (Chapter 6). At present, the capability of plants to take up this relatively insoluble form is not understood.[74] Jones et al.[87] have reported that lead uptake is enhanced by a deficiency of sulfate in the soil. In this study, the lead in rye grass tops was higher than that in the roots when the soil was deficient in sulfur.

Once lead enters the plant from the soil solution, most of it remains in the roots.[60,66,72,77] Distribution to other portions of the plant does occur, but it is uneven and variable among species.[71,72,77] Plant age and season of the year also affect internal distribution.[66,72] In all cases, the levels are quite low because of the small amounts of available lead in the soil solution.

8.2.2 Effects on Vascular Plants

Lead is a normal soil constituent, but it has not been shown to be essential for plant growth.[66,69] The response of plants to lead is therefore dependent on the extent to which normal metabolic processes are disturbed. Metabolic disturbances manifest themselves as growth abnormalities (the visible symptoms of which may be growth stimulation, stunting, yellowing or purpling of leaves) or, in the event of acute toxicity, senescence and death.[82] Metabolic disturbances are most likely to occur in response to high available lead levels and to highly soluble forms of lead entering the plant.[66,69]

Antonovics, Bradshaw, and Turner[88] state that lead uptake is constant with increasing levels of soil lead until a certain point is reached at which lead uptake becomes unrestricted and rises abruptly. Little is known, however, about the mechanism of lead uptake. Undoubtedly, lead in solution moves into the plant through the root hairs along with mineral nutrients and is translocated to other areas of the plant. The vascular tissue is the pathway of water in the root, through the stem, into the petioles, and into the leaf veins.[89] After entering the root hairs, water containing lead and nutrients must pass through the root cortex to reach the central core of vascular tissue. Because the movement of water through the cortex is from cell to cell with no specific pathway such as vascular tissue, lead possibly may not pass easily through cell membranes. This may explain why plant roots show higher lead contents than other plant organs. Malone et al.[90] have shown that some of the lead that enters the root is concentrated in dictyosome vesicles and subsequently moves via the vesicles to the cell wall, where fusion with the cell wall occurs.

Lead has been reported to have both a beneficial and an inhibitory effect on plant growth.[66,69] Brewer[69] cites studies in which lead nitrate resulted in increased nitrification and increased plant growth when added to the soil. However, when lead nitrate was added to solution cultures, retardation of root growth occurred. In neither case was the metabolic action of lead nitrate observed in the plants. The chemical identity of lead in plants is as yet not known.[60]

Most studies[60,66,69] that describe growth inhibition and plant toxicity caused by lead compounds are based on visible growth responses resulting from lead added to soils or to solution cultures and do not deal with specific metabolic processes.

The effects of lead compounds on such plant processes as photosynthesis,[60,91-93] mitosis,[1,60,66] and water uptake[92] have been reported. Miles et al.,[91] using isolated chloroplasts from spinach leaves, found that lead salts inhibit photosynthetic electron transport. Wong and Govindjee[94] have shown in isolated maize chloroplasts that lead salts affect photosystem I, inhibiting P700 photooxidation and altering the kinetics of re-reduction of P700. In laboratory studies, lead has been found to have a damaging effect on cell walls, nuclei, and mitochondria. Lead retarded cell proliferation but permitted an increase in size.[1] Spindle disturbances and chromatid formation in root tips of *Allium cepa* induced by lead nitrate have been found to be indistinguishable from those induced by colchicine.[1]

Miller and Koeppe[95] and Bittell et al.[96] studied the effects of lead on mitochondrial respiration. Lead effects are related to the phosphate status of the respiratory system as well as to the oxidation of nicotinamide adenine diphosphonucleotide monohydrogen (NADH). The lead levels used in this study approximated the levels found near heavily traveled highways. The form of lead used, $PbCl_2$, and the isolated mitochondria were not typical of field conditions, but lead in plants does associate with mitochondria and chloroplast membranes.[60,66,75]

The presence of lead in plants has also been shown to have indirect effects on plant growth. For example, absorption of phosphorus and manganese, two essential elements for growth, is inhibited when lead is present in the plant.[97] Lead may also contribute to copper deficiency in plants.[98]

The majority of the studies reporting lead toxicity have been conducted with plants grown in artificial nutrient culture. As a result of the studies, the concept has emerged that the effects of lead, whether stimulatory or inhibitory, depend on a variety of environmental factors, including associated anions and cations within the plant and in the growth media, and the physical and chemical characteristics of the soil itself. Because lead interacts with so many environmental factors, specific correlations between lead effects and lead concentrations are extremely difficult to predict.[60]

Lead toxicity has not been observed in plants growing under field conditions. This observation may be explained by the fact that ambient lead concentrations in the environment have not been high enough, except under unusual conditions (near mines and smelters) to cause a toxic effect or a decrease in crop yield.[60]

In summary, the effects of lead on vascular plants appear at this time to be minimal. The most important effects may be those resulting from ingestion of topical and internal plant lead by grazing animals (the next trophic level). From the standpoint of economic consequences, evidence developed on the effects of lead in agroecosystems indicates that topical lead contamination of plants is more likely to have economic consequences than internal lead (see Section 6.4.3).

8.2.3 **Effects on Nonvascular Plants**

8.2.3.1 MOSSES AND LICHENS

Mosses have been shown to have unique capacity for sorbing heavy metal ions to their surfaces. Traces of copper and lead are sorbed readily even in the presence of other metal ions (calcium, magnesium, potassium, sodium).[99] These ions are sorbed through the leaves of the moss because mosses have no root system for uptake of nutrients from soil or other substrates. Mosses also have neither epidermal cells nor a cuticle (waxy layer), so the internal parenchymal cells are readily exposed to substances from the air.[99,100] Accumulation of heavy metal ions in mosses is generally from precipitation, which is a very dilute solution of metals and water. The accumulation occurs because of the chemical complexes formed between these heavy metal ions in precipitation and negatively charged organic growth.[101]

Lichens, like mosses, have no roots; therefore all minerals are absorbed through the cell membranes. Mechanisms similar to those found in mosses may also be responsible for the uptake of metal ions by lichens. But lichen accumulation of lead is not as extensive as that in mosses.[101]

8.2.3.2 ALGAE

Trollope and Evans,[102] in a study of algal blooms in the Lower Swansea Valley, Wales, noted the sensitivity of algae to the heavy metal content of water. A marked difference was observed in the nature of algal blooms found in three different groups of waters at 12 different stations (Table 8-7). The algae most tolerant to high lead concentrations were: *Coccomyxa, Mougeotia, Tribonema,* and *Zygnema.* Less tolerant were *Microspora, Oscillatoria* and *Ulothrix,* and the least tolerant were *Cladophora, Oedogonium,* and *Spirogyra.* All of these algae were subject to contamination from run-off water and dust from the zinc smelter. The concentrations of lead in the plants varied among genera and within a genus. The uptake of individual metals by algal blooms appears to be regulated. Mean metal concentrations in the three groups of algae are ordered Fe >Zn >Pb >Cu >Ni, whereas the mean metal concentrations in the aquatic bodies were ordered differently: Adjacent to the source, Zn >Pb >Fe >Ni >Cu; near, Zn >Ni >Pb >Fe >Cu; distant (6 to 10 km), Fe >Zn >Ni, Pb >Cu. Concentrations of metals in the algae were directly related to the concentrations in the water, with the algae in the most polluted waters having the highest concentrations. No experiments were conducted to determine whether the algae found in the least polluted waters would grow in more polluted ponds.

Observations in the New Lead Belt of southeastern Missouri[103] have shown that relatively high concentrations of lead in stream bottom sediments do not have much effect on algal growth in these relatively hard natural waters. Under these conditions, the dissolved lead salts are in very low concentrations and well below the limits of tolerance of most

TABLE 8-7. CONCENTRATIONS OF SELECTED HEAVY METALS IN FRESH WATER AND IN FRESHWATER ALGAL BLOOMS[102]

Area of water	Concentrations in fresh waters, μg/ml Cu	Fe	Ni	Pb	Zn	Algal bloom	Concentrations in freshwater algal blooms, μg/mg Cu	Fe	Ni	Pb	Zn
Water adjacent to zinc smelting waste:											
1	0-03	0-24	0-15	0-31	34-1	Mougeotia	0-38	17-61	0-24	6-19	44-94
						Tribonema a	0-4	9-97	0-16	5-45	19-93
						Tribonema b	0-7	33-92	0-26	4-94	17-61
2	0-02	0-11	0-1	1-24	19-61	Tribonema c	0-67	23-37	0-29	3-68	21-11
						Tribonema d	1-33	30-6	0-24	14-19	17-44
3	0-01	0-25	0-12	0-1	11-44	Coccomyxa	0-65	49-51	0-15	3-23	19-05
						Zygnema	0-46	39-85	0-7	2-6	45-89
4	0-02	0-28	0-15	0-1	1-96						
Mean	0-02	0-22	0-13	0-44	16-78	Mean	0-66	29-26	0-29	5-75	26-57
Water near zinc smelting waste:											
5	0-02	0-27	0-12	0-1	1-96	Oscillatoria	0-34	2-8	1-07	0-58	1-88
6	0-05	0-56	2-2	0-31	4-9	Ulothrix	0-48	7-78	0-3	2-38	3-56
7	0-06	0-56	2-94	2-91	4-9	Microspora	1-02	42-31	0-11	2-16	9-26
Mean	0-04	0-46	1-75	1-11	3-92	Mean	0-61	17-63	0-49	1-70	4-89
Water distant from zinc smelting waste:											
8	0-03	0-39	0-07	0-1	0-21	Cladophora a	0-06	3-94	0-03	0-23	0-89
						Spirogyra a	0-22	3-03	0-13	0-4	1-59
						Spirogyra b	0-29	7-66	0-12	0-11	1-92
9	0-02	0-1	0-06	0-1	0-08	Oedogonium	0-11	0-7	0-07	0-06	0-12
10	0-01	0-39	0-12	0-1	0-08	Cladophora b	0-05	2-91	0-1	0-09	0-97
11	0-02	0-39	0-12	0-1	0-16	Spirogyra c	0-23	0-46	0-09	0-13	1-09
12	0-02	0-11	0-12	0-1	0-05	Spirogyra d	0-05	8-93	0-03	0-04	0-32
Mean	0-02	0-28	0-1	0-1	0-12	Mean	0-14	3-95	0-08	0-15	0-98

algae, including the sensitive *Cladophora*. Extensive blooms of *Cladophora* were observed in one stream where bound lead associated with the filaments exceeded 5000 ppm. These results indicate that lead chelated or bound to the cell envelopes apparently had no major physiological effect on algae under the existing natural conditions.

8.2.3.3 BACTERIA

The response of certain bacteria to lead has been studied by Tornabene and Edwards.[104,105] *Micrococcus luteus* and *Azotobacter* sp., when grown in lead-containing media under experimental conditions, were able to take up substantial quantities of lead with no apparent effects on cell viability. Most of the lead became associated with the cell membrane. Several studies[106,107] indicate that bacteria in lake sediments under anaerobic conditions react differently. Methylation of mercury and arsenic by microorganisms is a well-known phenomenon,[108,109] but the methylation of lead is not. The first evidence for the methylation of lead was demonstrated experimentally by Wong et al.[110] Microorganisms in lake sediments were able to transform certain inorganic and organic lead compounds into a volatile tetramethyl lead (Me_4Pb) when the sediment was enriched with nutrient broth and glucose to stimulate growth and growth occurred under anaerobic conditions. The Me_4Pb lead production was greatly increased when inorganic lead nitrate or organic trimethyl lead acetate (Me_3PbOAc) was added at 5 mg per liter of sample. The biological methylation from trimethyl lead (Me_3Pb) to Me_4Pb appeared to proceed quite readily. This conversion was demonstrated using pure species of bacterial isolates from lake sediments without the sediments being present. They were able to show that *Pseudomonas, Alcaligenes, Acinetobacter, Flavobacterium*, and *Aeromonas* sp. growing in a chemically defined medium could transform lead nitrate, lead chloride, and trimethyl lead acetate (Me_3PbAc) into volatile tetramethyl lead (Me_4Pb). None of the bacteria were able to convert insoluble lead to Me_4Pb. Schmidt and Huber,[107] however, have observed that Pb^{2+} can be biologically alkylated and transformed to Me_4Pb (see Section 6.4.2.2).

Generally, most naturally occurring bacteria can tolerate lead without toxicity.[104,110] However, there is wide variation in effects. For example, lead has been shown to stimulate growth of a bacterium identified as *Micrococcus flava* Strevisan,[111] producing an insoluble lead metabolite; but lead has also been shown to be widely inhibitory to aerobic activated sludge bacteria,[112] aerobic river water bacteria,[113] and marine sulfate-reducing bacteria.[114] These reports seem to indicate that lead has a relatively casual relationship with bacterial cells, with no specific inhibitory role; but this should be viewed with caution.

Previously, the presence of lead in estuarine sediments was mentioned. The methylation of lead in this environment and its effects on the biota existing there have not been studied.

Effects of the addition of 1000 ppm of copper, nickel, lead, and zinc on carbon dioxide release during aerobic incubation of soil alone and after treatment with straw were studied.[115] Carbon dioxide release during incubation from soils without added straw was decreased by all metallic elements. Carbon dioxide release from soil plus straw was decreased by lead. The toxic effects of the high concentration of elements on the activity of the microorganisms attacking organic matter were believed to be caused by the ability of the elements to compete with essential elements (manganese, iron, and zinc) for the active sites (SH, NH_2, = NH) of enzymes. Nickel and lead were slightly more inhibitory than copper and zinc.[115]

Cole[116] found that addition of lead to soil resulted in 75- and 50-percent decreases in net synthesis of amylase and α-glucosidase, respectively. The decrease in amylase synthesis was accompanied by a decrease in the number of lead-sensitive, amylase-producing bacteria, whereas recovery of synthesis (usually in 24 to 48 hr) was associated with an increase in the number of amylase-producing bacteria, presumably lead-resistant forms. The results indicated that lead is a potent but somewhat selective inhibitor of enzyme synthesis in soil and that highly insoluble lead compounds such as PbS may be potent modifiers of soil biological activity.

8.3 EFFECTS ON RELATIONSHIPS BETWEEN ARTHROPODS AND LITTER DECOMPOSITION

A study[117] of the impact of a lead smelting complex in southeastern Missouri focused on forest-floor litter arthropod fauna. Litter-arthropod food chains and the possible transfer of lead through plant-herbivore-carnivore food chains were studied as a means of detecting perturbations in this ecosystem. Both point and fugitive sources contributed to heavy metal levels in the study area. Lead, cadmium, zinc, and copper were the primary elements studied. Litter mass, heavy metal and macronutrient content (Ca, P, K, and Mg), cation exchange capacity, and pH were studied to characterize the arthropod food base. Arthropods were removed from litter by Von Tullgren funnel extraction. The arthropods were taxonomically classified according to their feeding habits or levels: detritivore, fungivore, littergrazer, omnivore, and predator. Level refers to the sequential location of a particular organism in the food chain or web. Their population density at each trophic level, biomass, and heavy metal and macronutrient content was determined.

Changes in litter decomposition and nutrient cycling were reflected in the population dynamics of litter arthropods and macronutrient pools. Reduced arthropod density, biomass, and richness (an estimate of maximum diversity) were observed. The macronutrients Ca, K, and Mg in the 01 and 02 litter layer at a site 0.4 km from the smelter were significantly reduced. Two litter layers or horizons are recognized by the Soil Science Society of America. The 01, or surface layer, is that in which dead plant material still retains its original conformation. The 02 layer is that layer in which the material is fragmented and no longer recognizable as to species or origin.

Mean heavy-metal concentrations were greater in the undecomposed 02 litter layer collected at 0.45 and 0.8 km from the smelter. The Pb concentration was 103,000 ppm; Zn was 4910 ppm; Cu was 6080 ppm; and Cd was 179 ppm. At these sites, heavy-metal concentrations correlated with 02 litter layer accumulations. A change from the normal was also noted in the cation exchange capacity and pH of the soil.

In summary, the results of this study[117] indicate that the dynamics of forest-nutrient cycling processes are seriously disturbed near these lead smeltering complexes.

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9. QUANTITATIVE EVALUATION OF LEAD AND BIOCHEMICAL INDICES OF LEAD EXPOSURE IN PHYSIOLOGICAL MEDIA

In this chapter, the state of the art regarding measurement of lead and biochemical markers of lead exposure is summarized, and the accuracy and precision of various methods of intra- and interlaboratory comparison are examined. The relative diagnostic merits of one type of measurement with respect to another — blood lead versus urinary lead, for example — are discussed elsewhere in the document.

9.1 GENERAL SAMPLING PROCEDURES FOR LEAD IN BIOLOGICAL MEDIA

The occurrence of lead in physiological media of interest in this discussion is at the trace level, even under conditions of marked exposure. Therefore, a number of sample collection and handling precautions are called for, both to minimize loss of lead from samples and to avoid the contamination of samples by this ubiquitously distributed element.

Sample-gathering problems are of special concern in blood lead screening programs in which great numbers of samples must be gathered, transported, and processed in the shortest possible time.[1] Sample collection details for blood lead and other biological indicators of exposure have been reviewed in the clinical literature.[2]

In blood studies it is often desirable to use capillary blood by finger prick instead of venous puncture, especially when young children are involved. A number of studies have shown that capillary and venous blood are essentially identical in lead content: Mitchell et al.[3] obtained a correlation factor of 0.92. However, it should be emphasized that such results can be achieved only when extreme care is used in cleaning the skin, and when contamination of capillary tubes and syringe is avoided.

A number of workers have used filter paper discs for blood sample collection as an alternative to handling discrete blood volumes. The paper for this purpose must be selected for uniformity of manufacture, low lead content, and uniform blood dispersal.

In the methods of Cernik and Sayers involving lead workers,[4,5] for example, whole blood obtained by finger prick is spotted onto Whatman No. 4 qualitative paper. Either 9.0-mm or 4.0-mm discs are then punched out and analyzed by the Delves cup microtechnique or the carbon-cup flameless atomic absorption procedure. These methods correlate well with blood obtained by venous puncture.

Joselow and Bogden[6] have employed a micromethod for routine mass screening of children using a paper disc-in-Delves-cup technique. Capillary blood is allowed to drop onto an 8.2-cm disc of Schleicher and Schwell No. 903 filter paper so as to form a spot somewhat larger than 1/4 in. in diameter, and discs of 1/4-in. diameter are punched out directly into previously conditioned Delves cups. A correlation coefficient of 0.9 was obtained when results of this method were compared with a macroprocedure using venous blood and the procedure of Hessel.[7]

Cook et al.,[8] in their investigation of capillary blood collected on paper and of blood volume gathered by venous puncture, obtained a correlation approaching 0.8.

Puncture-site preparation is also important in sampling. Marcus et al.[1] report that a preliminary cleaning with ethanolic citric acid solution followed by a 70-percent ethanol rinse is satisfactory, whereas Cooke et al.[8] chose to employ a vigorous scrubbing with low-lead soap solution and deionized water rinsing.

A second precaution with finger-prick sampling is the way in which the blood flow is expedited for sampling. Gravity flow or direct uptake (filter paper) is preferable to squeezing the finger tip, as hard squeezing might dilute the blood drop with tissue fluid.

Further precautions include the use of polypropylene syringes[9] with needles of stainless steel and polypropylene hubs for puncture sampling.

Urine-sample collection requires acid-washed plastic containers (and caps) and should include a low-lead bacteriocide if samples are stored.

Hard- and soft-tissue gathering from laboratory animals or human sources entail surface debridement of ambient lead encountered in the process of sampling. Hair cleaning before analysis may be carried out via the method of Hammer et al.;[10] bone and teeth may be given a quick rinse in EDTA solution. With soft tissue, the outer layer may be removed or a segment of underlying matter excised. For organs of heterogeneous morphology such as kidney, it may be more desirable to subject the sample to a quick rinse in an ionic chelant, such as EDTA, that does not penetrate beyond the outer membrane.

Regardless of specific methodology employed, all reagents used in lead determinations in biological media should be certified for low-lead content; and samples should be stored in a manner that minimizes lead contamination from air or surfaces. Standard lead solutions should be prepared frequently, either from stock solutions from analytically certified sources or from the pure metal. Solution preparation in glass should be minimized, particularly when analysis is at the sub-part-per-million level.

9.2 BLOOD LEAD

The first generally accepted practice for measuring lead in blood and other biological media involved a spectrophotometric technique based on the binding of lead with a chromogenic agent to yield a chromophoric product. In this connection, the classic ligating agent has been dithizone-1, 5-diphenylthiocarbazone. The lead dithizonate is measured spectrophotometrically at 510 nm.

Two reliable variations of the spectrophotometric technique when dealing with lead content of 1 to 10 ppm are the USPHS and APHA procedures.

The USPHS assay[9] is a double-extraction, mixed-color procedure having bismuth as the chief interferent. Blood (and urine) samples are wet-ashed using concentrated nitric acid certified as to low-lead content. After digest treatment with hydroxylamine and sodium citrate, the pH is adjusted to 9 to 10, and cyanide ion is added. Formation and extraction of lead dithizonate is carried out using a chloroform solution of dithizone. Lead is then re-extracted into dilute nitric acid (1:99 water), and the aqueous layer is treated with ammonia-cyanide solution and re-extracted with dithizone-containing chloroform. The organic extracts are read in a spectrophotometer at 510 nm. Although bismuth interferes, this element is encountered infrequently in biological media.

The APHA procedure[11] varies from that described above mainly in permitting removal of bismuth at pH 3.4 as the dithizonate.

At present, the colorimetric method has been largely supplanted by two other techniques: atomic absorption (AA) spectrometry in all its variations and anodic stripping voltammetry (ASV).

Of these two analytical approaches, the more technically popular, by far, is AA spectrometry, which is used for both macro- and micro-scale analyses. The theoretical basis for AA and its instrumental design are beyond the scope of this presentation; basic reviews are provided by Christian and Feldman[12] and by L'Vov,[13] however.

Macro-scale AA analysis involves direct aspiration of suitably treated lead-containing samples into a flame for lead-atom generation and excitation. Micro-AA, which is being used more widely as accessories and instrument refinements become commercially available, is of two types: flame and flameless, with the latter employing thermoelectric systems in lieu of a flame.

Of the flame microtechniques for AA analysis of blood samples, the most widely used is Delves cup procedure[14] in which small volumes of blood, 10 to 100 μl, are placed in lead-free nickel crucibles. After the organic matrix is destroyed, the cups are inserted into a flame. The overall configuration of the system permits the optical path to be maximally occupied by the lead atom population originally present in the sample. Destruction of the organic matrix in blood may be either partial, using hydrogen peroxide, or total, with pre-ignition of the organic matter caused by placing the cups near the flame.[15]

Increasing use is being made of flameless AA, particularly the heated graphite furnace accessory, whereby volumes of blood are reduced to ~ 1 μl, and also whereby *in-situ* destruction of organic matter may be achieved.

The electrochemical technique known as ASV[16] is also coming into common use in a number of laboratories, particularly for blood and urine lead analysis. As developed by Matson and Roe,[16] the technique involves concentrating an ion such as divalent lead on a negative electrode during a predetermined plating time (5 to 60 min) followed by polarity reversal and increase for short periods to yield a discrete current peak that is proportional to ion concentration.

Also in current use are X-ray fluorescence spectrometry and neutron-activation analysis, two sophisticated instrumental methods for trace analysis. The considerable expense of the equipment and the amount of operator expertise involved rather limit their use to that of regional service facilities or central laboratories. The two methods have a distinct advantage, however, in that they permit multiple-element analysis, a feature that will be of increasing importance as more is unveiled about the complex interactions of lead with other metals in man and other organisms.

9.3 URINE LEAD

Precautions to be taken for urine sample collection were noted earlier. Because of the considerable amount of ionic matter in urine, it is usually necessary to manipulate urine samples in various ways before analysis.

All of the methods employed for blood lead analysis as described above may also be applied to assessment of urine lead levels. Care, however, should be exercised in the analysis of urine samples from patients undergoing chelation therapy, with special attention to how a specific procedure will accommodate or be interfered with by lead excreted as a complex, e.g., lead-EDTA. Prior ashing of urine samples will minimize complications in this regard, but partial degradation or no prior treatment might necessitate co-analysis of lead in the complex form for standards.

9.4 SOFT-TISSUE LEAD

Because of the nature of this medium, it is usually necessary either to ash or to solubilize tissue samples. Wet-ashing is rapid and avoids lead loss via volatilization, but it requires use of corrosive acids and procedural care to avoid contamination of reagents and other problems. Dry ashing, on the other hand, is simple and uses no contaminating reagents. The drawbacks are mainly those of lead volatilization and retention of the element in refractory residues. Newer techniques of ashing include (1) low-temperature ashing, in which dry samples are mineralized in an evacuated chamber that is bathed in an energy-rich plasma via r-f discharge in an oxygen stream, and (2) use of the combustion bomb, in which samples are heated in acid an at elevated temperature in a sealed inert vessel.

A newer method of tissue handling, solubilization, entails the treatment of samples with quaternary ammonium compounds and analysis of aliquots, chiefly by AA spectrometry.[17]

The bulk of the current literature centers on the use of atomic absorption spectrometry as the method of choice for assessing lead levels in soft tissue.

9.5 HAIR LEAD

An attractive feature of the clinical use of hair-lead levels is its noninvasive nature and the feasibility of assembling a rough time frame for lead exposure by isolating discrete segments of the total hair length.

A serious drawback in hair analysis, however, is the level of contamination by ambient air lead, lead in hair preparations, etc., as discussed by Hammer et al.[10] Hair measurements without prior treatment of the sample include both exogenous and endogenous sources. Examples of the former are dyes, shampoos, sweat, and dust. Pre-analysis hair washing with detergent and EDTA removes most of the externally found lead; but there is still no definitive way to determine whether any cleaning technique removes the contamination portion of lead and leaves the internal lead content undisturbed.

Hair is usually wet-ashed before analysis, and the digest is diluted and analyzed by AA spectrometry. Because relatively high levels of lead are encountered in hair, small sample sizes can be used when a sensitive procedure such as AA spectrometry is employed.

9.6 LEAD IN TEETH AND BONE

The biochemical significance of lead levels in teeth and bone is discussed elsewhere. From an analytical standpoint, bone samples are usually obtained from experimental animal studies. Bone samples must first be debrided of muscle and connective tissue and chemically rid of surface lead contamination by rinsing with EDTA or other chelant solution.

Bone and teeth are usually wet- or dry-ashed before analysis, and the relative merits of these mineralizing procedures are as noted above with soft tissue assays. Because of the high mineral content of bone and teeth, care must be taken to avoid spectrochemical interference by calcium, phosphate, etc. The relatively high levels of lead in these two hard tissues, however, permit dilution of the samples for testing. Because the effect of the high mineral content on analytical signals is probably sufficient to preclude the use of simple aqueous lead standards, it is advisable to employ workup solutions of bone samples that have first been analyzed for lead content and to which known amounts of lead from a stock solution are then added. Matrix standards prepared in this fashion are assumed to reflect the influence of mineral content on all of the samples.

9.7 COMPARATIVE STUDIES OF METHODS FOR MEASUREMENT OF LEAD IN BIOLOGICAL MEDIA

In an interlaboratory study of the USPHS colorimetric method for lead in blood and urine, Keenan et al.[18] reported the results from 10 participating laboratories. For blood, a mean lead value of 26 ± 0.82 μg/dl was obtained; spiked samples gave virtually identical correspondence among the groups. Urine samples with lead added gave values from the reporting groups with a mean of 679 ± 5.5 μg/liter.

Microscale AA techniques for whole-blood lead have been found to show good correspondence with results obtained using conventional flame procedures.[19,20]

Matson[21] has reported good correlations for lead levels in blood and urine when comparing ASV with a colorimetric and an AA procedure. Similarly, Horiuchi et al.[22] saw little difference in lead levels for blood and urine when contrasting ASV, AA, and polarography.

Interlaboratory studies of various methods for lead analysis of biological media have yielded somewhat disappointing results.[23-25] In a recent study involving 66 laboratories throughout Europe, blood and urine determination variance was observed to be unacceptably high.[25]

Presently, the Center for Disease Control (CDC) is carrying on a monthly proficiency testing program for blood lead involving approximately 200 laboratories. Results are made available through monthly reports for analysis of bovine blood samples.[26] The criterion used by CDC for assessing unsatisfactory performance is: greater than 15 percent relative deviation at levels of 40 μg/dl or above and greater than 6 μg/dl at lower levels.

In a recent CDC report (Survey 1977I)[27] covering 130 laboratories for testing and 26 reference laboratories using three bovine blood samples (cows fed lead acetate), 72 percent of the tested laboratories were within the acceptable range for a sample having a mean of 16.6 μg/dl. The acceptable percentage was lower, interestingly, at higher sample means of 48.2 and 54.6 μg/dl (64 and 67 percent, respectively). When results were tabulated as a function of method, the Delves cup AA spectrometric and ASV methods furnished the smallest coefficients of variation.

A number of other proficiency programs are presently operating in the United States, and the results of these have been included, along with the European program, in a recently published monograph by Pierce et al.[2] These same authors describe the state of the art critically and offer some recommendations for improving the quality of blood lead analyses:

1. Every laboratory should have established quality-control procedures.
2. Control procedures should include replicate analyses, recovery of known additions or spikes, participation in interlaboratory tests, and analyses of known materials.
3. Testing samples that the analysts analyze blind should be used to minimize bias.

It has been suggested[28] that the acceptable agreements in blood lead levels found when a single laboratory employs different techniques compared with the wide variance found when different laboratories employ different methods on portions of common blood samples relate primarily to preparation and state of the blood samples before and during distribution and subsequent analysis. The results of Grimes and coworkers[29] bear this out because a large number of carefully controlled blood samples analyzed by their laboratories, using the paper disc technique, provided results that compared well with those of other laboratories using other instrumentation with the disc technique.

9.8 MEASUREMENT OF URINARY δ-AMINOLEVULINIC ACID (ALA-U)

Some comments regarding sample collection for ALA-U are necessary. ALA is stable in acidified urine (pH 1 to 5), so that acetic or hydrochloric acid addition is satisfactory at the time of sample collection. If samples are stored in the dark at 4°C, the ALA content remains relatively constant for several months.[30]

ALA-U measurement usually entails the classic method of Mauzerall and Granick.[31] In this approach, ALA-U is condensed with a β-dicarbonyl compound such as acetylacetone or ethyl acetoacetate to yield a substituted pyrrole derivative; this intermediate is then caused to react with Ehrlich reagent (*p*-dimethylaminobenzaldehyde) to yield an intense ionic chromophore. This procedure is not specific for ALA-U, however, since aminoacetone interferes. Though the significance of such interference is marginal when ALA-U levels are markedly elevated, it becomes very important when only slight elevations of ALA-U are being measured.

First, urine samples are chromatographed on ion-exchange resin columns (Dowex-2), the ALA-U being co-eluted with urea using water as eluent. Eluate transfer to a Dowex-50 column is followed by sequential elution with water to remove the urea and then with acetate solution to permit removal of the ALA-U. Treatment with acetylacetone and heating to effect complete condensation is followed by treatment of sample aliquots with modified Ehrlich reagent (*p*-dimethylaminobenzaldehyde in perchloric/acetic acid). The resulting chromophoric salt is allowed to achieve maximum intensity (*ca.* 15 min) after which the sample is read in a spectrophotometer at 553 nm. The detection limit is 3 μmoles/liter urine, and chromophore stability is limited to about 15 min.

A number of modifications to the above basic approach have been reported. Several reports attempt to take into account the interference posed by aminoacetone. The quantitative corrections to be used are described by the authors of these reports.[32,33]

The initial isolation of porphobilinogen is omitted (in cases where porphyria is not suspected) in the modification of Williams and Few,[34] in which a correlation of 0.99 was observed with the reference technique using samples from 39 lead workers. Doss and Schmidt[35] report that use of commercially available dual ion-exchange columns offers results that compare favorably with the Mauzerall and Granick method.[31]

The assay has been automated with good correspondence of results to the manual method in the laboratories of Grisler et al.[36] and Lauwerys et al.[37]

In another variation of the ALA-U procedure, the method of Schlenker et al.[38] removes aminoacetone which interferes with the assay. In the procedure of MacGee et al.,[39] urinary and blood ALA is determined by gas-liquid chromatography, a highly specific technique.

9.9 MEASUREMENT OF δ-AMINOLEVULINIC ACID DEHYDRATASE (ALA-D)

Located in erythrocytes, δ-aminolevulinic acid dehydratase (ALA-D) catalyzes the conversion of ALA to porphobilinogen in the heme biosynthetic pathway. Its inhibition by heavy metals such as lead indicates that it is a sulfhydryl enzyme and also forms the biochemical basis for assessing its activity in lead-exposed organisms.

Blood collection requires the use of low-lead tubes containing anticoagulant, whereas for micromeasurement, blood is collected in a heparinized microhematocrit tube.[40] Obviously, use of strong chelants, such as EDTA, as anticoagulants is not advisable because competition for lead may reactivate the lead-inhibited enzyme.

Minimal time lapse should occur between collection and enzyme assay—no more than 24 hr if samples of heparinized blood are held at 4°C.

The chemical basis for measuring enzyme activity involves spectral measurement of the amount of porphobilinogen generated from ALA, the porphobilinogen being condensed with *p*-dimethylaminobenzaldehyde to yield a chromophore that is measured at 553 nm. Mercury (II) is employed to minimize the interference effect of sulfhydryl entities present in the medium.

The micromethod of Granick and co-workers[40] requires only 5 μl of whole blood and appears to be of value in a screening program. Enzyme incubation is done at 37°C for about 60 min; ALA of the highest possible purity is necessary as a substrate.

Termination of the reaction (enzyme activity) is done via trichloroacetic acid.

The activity of the enzyme may be calculated in two ways:[40,41]

$$\text{Activity} = \Delta OD_{553}(\text{sample-tissue control}) \times \frac{138{,}000\ \text{nMol}}{\text{HCl}}\ \text{PBG/ml RBC/hr}$$

$$= \Delta OD_{553}(t_{60}' - t_0') \times \frac{100}{\text{HCL}} \times 131.48\ \text{nMol PBG/ml RBC/min}$$

In the European standardized method for ALA determination[42] aimed specificially at enzyme levels in blood corresponding to low levels of exposure to environmental lead, incubation of the enzyme in three aliquots of blood (0.2 ml cooled to 4°C) is carried out in the presence of excess δ-aminolevulinic acid. An aliquot blank is also carried through the procedure. Hemolysis of the cells and incubation with substrate is followed by quenching with mercuric chloride-trichloroacetic acid solution. Centrifugation and treatment with modified Ehrlich's reagent is followed at 5 min by absorbance measurement. Blood samples are preferably run within 3 hr and in no case after 24 hr when held at 4°C.

In a study by Granick et al.[43] the activity of ALA-D before and after treatment with dithiothreotol (DTT) is determined. The DTT (added *in vitro,* 20 mM) provides -SH groups and reactivates the enzyme completely at all concentrations of blood lead. Because DTT-reactivated ALA-D yields total enzyme activity, variation in levels of the unactivated enzyme may be normalized by determination of the rates of both activities. Hence a person having a high ALA-D for genetic reasons at a given blood level of lead will have relatively high activity for both activated and nonactivated enzyme, and the activity ratio will depend less on genetic factors than on lead inhibition. Consequently, correlation is markedly improved. This study also shows that inhibition by lead is of the noncompetitive type.

9.10 MEASUREMENT OF FREE ERYTHROCYTE PROTOPORPHYRIN (FEP)

Another reaction that lead inhibits in the human heme biosynthetic pathway is heme formation. As a result of blocking this reaction, porphyrins, particularly protoporphyrin IX (actually zinc-protoporphyrin), accumulate in the erythrocytes. Measurement of protoporphyrin IX specifically, or all erythrocyte prophyrins together, is generally referred to as the free erythrocyte protoporphyrin (FEP) test.

The spectrochemical properties of FEP that form the basis for its measurement include its lability to light and strong acids, its metal coordinating ability, its possession of an absorption spectrum in the Soret band region, and its marked intensity of fluorescence. Spectral methods used, however, must take into account the fact that copro- and uroporphyrin provide considerable interference in FEP measurement. Although both absorption spectrophotometric and fluorometric methods may be employed for FEP assessment,[44-46] fluorometric techniques carried out on a microscale are more frequently used because of the relatively cumbersome nature of absorption spectrometry in terms of time and materials. These microfluorometric techniques, in particular, provide a rapid, relatively accurate means of screening pediatric populations.

In the microtechnique of Granick et al.[47], several microliters of whole blood are placed in 1-ml test tubes that also serve as fluorometric cuvettes. Addition of ethyl acetate/glacial acetic acid (2:1) is then rapidly followed by treatment with 0.5N HCl and vigorous shaking. The acidic phase (bottom layer) contains the bulk of the porphyrins. The cuvettes are scanned over the range 560 to 680 nm, using excitation at 400 nm. The ratio of the two-band maxima at 605 and 655 nm is measured for each sample with a ratio of 2:1 indicating only FEP. Any lesser value indicates copro- and/or uroporphyrins. In the latter case, an extraction with 0.05N HCl on analysis of a second sample removes copro- and uroporphyrin.

The technique of Piomelli,[48] using 20 μl of blood added to a 5-percent Celite suspension in saline, uses essentially the same initial extraction procedures as those noted above, but it is varied to employ 1.5N HCl to generate the fluorescing acid layer. Measurement is at 610 nm and excitation at 405 nm with coproporphyrin employed as the standard.

Observing that FEP is actually the zinc complex (ZPP), Lamola and coworkers[49] have devised a rather rapid and sensitive fluorometric procedure in which 20 μl of whole blood is worked up in a detergent-phosphate buffer solution (dimethyldodecylamine oxide) and fluorescence measured at 594 nm with excitation at 424 nm.

In the procedure of Chisolm and Brown,[50] which has been evaluated as a selected method by Schwartz and Piomelli, 20-μl blood volumes are treated with ethyl acetate/acetic acid solution (3:1) and agitated for 30 sec. After centrifugation, the layers are extracted with 3N HCl, and the acid layer is diluted with more 3N HCl. The acid extracts are analyzed spectrofluorometrically with coproporphyrin employed as the quantitating standard.

A portable hematofluorometer that utilizes front-face optics, internal standards, and built-in computational capabilities permits the assessment of erythrocyte zinc protoporphyrin (ZPP). As developed by Bell laboratories[51] and subsequently made available commercially,[52] the apparatus permits the analysis of a drop of blood applied to a cover slip directly from finger pricking. The ZPP level (μg ZPP/dl blood) is automatically calculated and displayed on a digital readout.

A number of micromethods for FEP analysis have been critically evaluated by Hanna et al. [53]: Double extraction with ethyl acetate/acetic acid-HCl,[48] single extraction with ethanol, single extraction with acetone,[54] and direct solubilization with detergent buffer.[49] Of these, the ethyl acetate and ethanol procedures were satisfactory; the complete extraction of FEP makes the former the technique of choice when an absolute value rather than technical simplicity is of primary concern.

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10. METABOLISM OF LEAD

10.1 INTRODUCTION

The metabolism of lead in man may be defined as the physiological processes relating to absorption, distribution, translocation, and net retention. The metabolism of lead in man is discussed in this chapter in terms of routes of exposure and of the physiological distinctions, existing within population classes, that modify metabolic processes, especially with reference to children versus adults.

Most of the material discussed in the following pages addresses the dietary habits of adults in the United States. For children, however, there are dietary habits that are distinct from those of adults and that have implications for differences in exposure between adults and children.

For example, in assessing the indirect contribution of airborne lead to diet, one must consider the hand-to-mouth activity of young children, i.e., sucking of dirty fingers in contact with environmental dust and dirt; retrieving foodstuffs, such as lollipops, that fall into dirt; and a host of other childhood activities by which airborne lead may contribute to the intake of lead by children but not by adults.

In this chapter, the physiological processes that control the uptake of lead by man (absorption) will be discussed first. Then the movement of lead through the body into its depot tissues (distribution) and its eventual elimination (excretion) will be treated.

10.2 ABSORPTION

The quantities of lead absorbed from environmental sources are determined not only by the amount ingested or inhaled but also by the particle size and chemical species involved.

Absorption depends also on specific host factors such as age, nutrition, and physiological status. In addition, the total quantity ingested in food and water varies greatly from individual to individual, and the total quantity inhaled depends on the size and weight of the individual and on the energy expended in day-to-day activity.

10.2.1 Respiratory Absorption

The International Radiological Protection Commission (IRPC) Task Group on Lung Dynamics[1] developed a model designed to predict the percentage of inhaled aerosols that would be deposited and retained in the lungs. This model predicted that approximately 35 percent of the lead inhaled in general ambient air would be deposited in the airways. Since the aerodynamic diameter of lead particles is generally in the range of 0.1 to 1.0 μm, deposition would occur predominantly in the deeper regions of the lung. Emissions from stationary sources frequently include a significant proportion of larger particles that, when inhaled, would be deposited primarily in the nasopharynx. Because these particles usually fall out of the air rather quickly, exposure to these larger particles is limited primarily to the near vicinity of the emission source. The deposition within the respiratory tract of very small particles (<0.1 μm) apparently occurs chiefly by diffusion,[2] and rates or sites cannot be predicted. The IRPC model predicts a total airway deposition of 40 to 50 percent for 0.5 μm particles, but a study in human volunteers indicated only 6 to 16 percent desposition, depending on the rate and depth of respiration.[3] Chemical composition also affects uptake as does the aging of the aerosol (Chapter 6). This illustrates the difficulty in choosing the appropriate chemical composition[4] for studies on deposition.

Airway clearance of lead aerosols as predicted by the IRPC lung model[1] is even more tenuous than are predictions regarding deposition. The model indicates that the absorption or clearance of lead deposited in the airways would vary greatly depending on the solubility and on the inherent toxicity of the particles to the clearance mechanism (lung macrophages and cilia).

10.2.1.1 HUMAN STUDIES

Actual studies on the fractional deposition of particles in the respiratory tract of man have not been extensive, especially in the case of lead. Using an air lead level of 150 μg/m^3, Kehoe[5-7] studied the deposition of combusted tetraethyl lead in human volunteers. The source of lead was combusted tetraethyl lead, which produced lead (III) oxide (Pb_2O_3) in the air. Subjects breathed air containing 150 μg/m^3 lead; the smaller particles averaged 0.05 μm in diameter and the larger ones averaged 0.9 μm in diameter, as viewed under the electron microscope. This represents a mass median equivalent diameter of approximately 0.26 and 2.9 μm, respectively.[8] Thirty-six percent of the smaller particles and 46 percent of the larger particles were deposited.

Nozaki[9] reported that when lead fumes generated in a high-frequency induction furnace were inhaled at a concentration of 10,000 μg/m^3 deposition was related to respiration rate and particle size. At 10 respirations per minute, the deposition decreased from 63 to 42 percent as the particle size was reduced from 1.0 to 0.05 μm. At 30 respirations per minute, deposition rates were about halved. The results, which are similar to those of Kehoe,[5-7] are fairly consistent with the IRPC lung deposition model.[1]

These data suggest that a 30 ± 10-percent deposition rate can be expected in individuals breathing ambient air and that deposition may vary considerably, depending on the particle size and the frequency of respiration.

The rate of lung clearance has been studied by means of gamma-ray lung scans following inhalation of ^{212}Pb, but the relevance of the results to the rate of clearance of the chemical and physical forms of lead usually inhaled by man is highly questionable.[10] These studies involved the absorption of ^{212}Pb atoms on carrier aerosol particles; however, desorption under these artificial circumstances may be totally unlike the clearance rate for ambient air lead particles.

Kehoe[5-7] reported a substantial increase in fecal excretion when large-particle lead oxide aerosols were inhaled for many weeks at 105 μg/m^3; the increase probably resulted from the swallowing of particles trapped in the nasopharynx. When air with a similar lead concentration in small particles was inhaled, only a small rise in fecal lead excretion was observed.

In a recent study, Chamberlain et al.[11] found a 35-percent rate of deposition, at a respiration rate of 15 per minute, when subjects inhaled automobile exhaust fumes containing radioactively labeled tetraethyl lead (^{203}Pb). This compares favorably with Nozaki's previous findings.[9] These authors[11] calculated that under conditions of chronic airborne lead exposure roughly 50 percent of the deposited lead is absorbed. Although alveolar macrophages ingest particles deposited in the lungs, these cells may be damaged by inorganic lead compounds.[12] Such damage has been demonstrated in rats and guinea pigs. It is possible, then, that lung defense mechanisms may be impaired when air contains high lead concentrations.

10.2.1.2 ANIMAL STUDIES

Animal studies by Bingham et al.[13] have demonstrated a pronounced reduction in the number of lung macrophages resulting from inhalation of lead oxide at both 10 and 150 μg/m^3. Similar results have been reported by others.[12,14,15] This suggests that the lung clearance mechanism may function less effectively when air lead concentrations are high. Thus, Pott and Brockhaus[16] reported that large doses of lead bromide solution or lead oxide suspension administered intratracheally to rats (1.5 mg of lead oxide per dose on 8 successive days) were retained by the body as completely as were intravenous doses. At one-third the dose, however, retention via the intratracheal route was significantly less.

Randall and his coworkers[17] exposed 4 baboons to aerosolized lead (Pb_3O_4) of varying particle size (mass median diameters of 5.9, 3.2, and 2.0 μm, respectively). The air lead concentrations varied from approximately 1 to 4 μg/m^3. The exposure period lasted 4 weeks, and blood sampling continued for 6 weeks. The rate of absorption of lead into blood was faster and reached a higher level for coarse (mean diameter = 1.6 μm) particles than for fine (mean diameter = 0.8 μm).

10.2.2 **Gastrointestinal Absorption**

10.2.2.1 HUMAN STUDIES

It must be noted at the outset that the absorption of lead from food varies with the physical form of dietary intake. For example, the literature indicates that the percent absorption of lead from beverages is about five to eight times greater than that from solid food.[18-20] Kehoe[5-7] concluded from long-term balance studies that approximately 10 percent of the intake of lead from food and beverages was absorbed from the gastrointestinal tract since this was the amount excreted in the urine. This estimate, however, disregarded the urinary lead that might have come from inhalation, as well as the lead excreted in feces after absorption from the gastrointestinal tract.

Rabinowitz et al.,[21] however, obtained similar results using orally administered ^{204}Pb incorporated into the diet.

Alexander et al.[22] studied the absorption of lead from the gastrointestinal tract in 8 infants and young children aged 3 months to 8.5 years and concluded that 53 percent of ingested lead was absorbed. Absorption and retention were consistent within the age range studied. This study, however, has been criticized because the values varied greatly.

In a recent study, Ziegler et al.[23] showed that a greater percentage of intake lead was absorbed and retained by infants than by older subjects. In this report, 2 separate series of investigations were conducted. In the first, 3 to 8 balance studies were performed with 9 infants each. In the second, each of 6 infants consumed randomly allocated diets providing low, intermediate, and moderate amounts of lead. When intakes of lead exceeded 5 μg/kg/day, which is a reasonable level given typical dietary patterns, net absorption averaged 42 percent and retention averaged 32 percent of intake. It should also be noted that there was an inverse relationship between calcium intake and blood lead level.

These results are in general agreement with animal studies and to some extent corroborate the findings of Alexander et al.[22] The study of Ziegler et al.[23] appears to be much better designed than that of Alexander et al.[22]

Ingested or dietary lead is often thought of as reaching a subject via a distinctly different route of exposure than inhaled lead. Inhalation of lead may be regarded as direct exposure to airborne lead. Some portion of dietary lead may also be attributed to exposure to airborne lead, but indirect rather than direct, with lead reaching food either by deposition onto aerial edibles or by fallout onto soil and subsequent absorption by root crops. (Internal translocation of lead between roots and aerial parts is apparently small.) In addition, variable fractions of inhaled lead are ingested after deposition in the airways; they are cleared by retrograde movement to the pharynx, where the particles are then swallowed.

Section 7.4.1 cites lead concentrations typically found in various foods, but no research has been brought to light that clearly partitions the origins of food lead. There would seem to be three principal candidates: (1) deposition of airborne lead (on primary food crops and on animal feed crops); (2) absorption of soil lead (much of this lead is often the historical accumulation of airborne fallout); and (3) lead acquired in the processing and canning of foods.

Based on the contrasts between fresh and processed foods (excluding frozen foods), it would appear that processing and canning of certain foods regularly doubles or triples their average lead concentrations (Table 10-1).

TABLE 10-1. LEAD CONTENT OF FRESH, PROCESSED, AND CANNED FOODSTUFFS[24]

Food	Lead concentration (ppm)	Food	Lead concentration (ppm)
Fresh produce		Canned vegetables	
Carrots	0.205	Beets	0.381
Lettuce	0.130	Beans	0.318
Potatoes	0.050	Peas	0.425
Avg.	0.128	Tomatoes	0.710
		Avg.	0.458
Processed foods		Canned juices	
White flour	0.052	Tomato	0.338
Cornmeal	0.143	Vegetable	0.215
Rice	0.104	Orange	0.135
Cereal	0.107	Fruit	0.251
Sugar	0.031	Avg.	0.235
Avg.	0.087		
Processed meats		Canned fruits	
Hot dogs	0.446	Peaches	0.417
Hamburger	0.578	Pineapple	0.402
Avg.	0.512	Applesauce	0.320
		Avg.	0.380
Fresh meats			
Beef	0.120		
Chicken	0.191		
Liver	0.150		
Avg.	0.154		

The data on lead in foods are not comprehensive enough to permit construction of a spectrum of levels ranging from fresh to canned and characterization of the resulting lead exposure. It must suffice to state at this point that some fraction of dietary lead probably is indirectly of airborne origin.

10.2.2.2 THE RELATIONSHIP OF ORAL INTAKE TO BLOOD LEAD LEVELS

It has been demonstrated repeatedly that blood lead levels increase when the oral intake of lead increases, but a quantitative expression of this relationship has not been determined. Studies from various parts of the world, as noted below, have shown that the increase in the blood lead for each 100 μg of lead ingested daily ranges from less than 6 to more than 18 μg/dl.

It is important to point out that the high end of this range was gathered using subject groups whose dietary intake may be of questionable relevance to the general population. Tepper and Levin[25] employed adult females in their study while Coulston et al.[26] used an adult prison population. These findings are not only in contrast to those from earlier U.S. studies but also to the results of a number of European studies based on the general population.[27] The European data are more consistent with a contribution of about 6 μg/dl to the blood lead level per 100 μg daily oral intake of lead; a similar level is reported by Kehoe.[5-7]

Children, particularly infants, absorb a larger percentage of lead than do adults. Consequently, the contribution of dietary lead to blood lead levels probably is less for adults, but definitive data are not available.

10.2.2.3 ANIMAL STUDIES

The absorption of lead from food and changes in absorption with age have been investigated in many animal studies; the usual values found ranged between 5 and 10 percent. However, Kostial et al.[28] demonstrated that 5- to 7-day-old rats absorb at least 55 percent of single oral tracer doses of ^{203}Pb, and Forbes and Reina[29] reported that in rats the gastrointestinal absorption of tracer doses of ^{212}Pb, ^{85}Sr, and ^{59}Fe was high prior to weaning but decreased rapidly thereafter. The absorption rate for lead was 83 percent at 16 days; it then decreased gradually to 74 percent on the day of weaning (22 days) and rapidly thereafter to about 16 percent at 89 days. Although there may be some question about the applicability of these data, they are consistent with results reported from studies of young children.

Kello and Kostial[30] have shown that milk increases lead absorption in 6-week-old rats. Fasting enhances lead absorption in mice.[20] Low dietary levels of calcium, iron, zinc, copper, selenium, and vitamin D have been reported to enhance lead absorption.[31,32] It has also been demonstrated that rats on an iron-deficient diet accumulate more lead in their bodies than do rats on an iron-sufficient diet.[33] Table 10-2 presents the data of Barltrop[34] relating to the effects of various nutritional factors on lead absorption as reflected in blood lead levels. It should be noted that these studies are short term studies obtained over a period of 48 hr.

TABLE 10-2. EFFECT OF DIFFERENT DIETS ON LEAD ABSORPTION EXPRESSED AS THE RATIO OF MEAN RETENTION FOR EXPERIMENTAL AND CONTROL SUBJECTS[34]

	Ratio of mean retention of lead (experimental : control)			
Diet	Blood	Kidneys	Femur	Liver
Low protein	5.1	2.5	2.8	2.2
High protein	1	3.7	2.6	1
Low fat	1	1	1	1
High fat	9.6	7.6	4.8	4.2
Low minerals	17.7	11.9	13.7	8.8
High minerals	0.2	0.2	0.1	0.1
Low fiber	1	1	1	1
High fiber	1	1	1	1
Low vitamins	1	1	1	1
High vitamins	1	1	1	1

The absorption of lead in paint chips has received attention because of the risk for young children who tend to ingest this material. Recent data from rat studies indicate that lead chromate and lead naphthenate incorporated into dried paint films are substantially available for absorption, although the absorption rate is 30 to 50 percent what it is for lead naphthenate in oil or for lead nitrate in aqueous solution.[35,36] The absorption of lead as a function of chemical form is shown in Table 10-3.[37]

TABLE 10-3. PERCENTAGE ABSORPTION OF DIFFERENT LEAD COMPOUNDS RELATIVE TO LEAD ACETATE[37]

Lead compound	Absorption, %
Control (no lead)	4
Metallic lead (180 to 250 μm)	14
Lead chromate	44
Lead octoate	62
Lead naphthenate	64
Lead sulfide	67
Lead thallate	121
Lead carbonate (basic)	164

10.2.3 Cutaneous Absorption

Absorption through the skin is of importance only in the case of organic compounds of lead, particularly the lead alkyls and lead naphthenates.[38,39] Soon after tetraethyl lead was introduced into commercial use, Eldridge[39] reported that it was absorbed through the skin with great facility in both dogs and guinea pigs. The presence of gasoline has been said to delay the penetration of tetraethyl lead through the skin,[40] although it has no effect on its uptake by the lungs.[41] In rats, five cutaneous or subcutaneous applications on alternate days of lead acetate or lead naphthenate produced, compared with unexposed animals, a decrease in ALAD in liver, a decrease in liver and body weight, and distribution of lead in assayed body tissues. Lead content was highest in kidney. Lead naphthenate was considered by the investigators to be more toxic than lead acetate because of more pronounced skin reactions, higher lead accumulation in brain, and the occurrence of a paralytic syndrome before death in two animals.[42]

The rate of absorption of tetraethyl lead and inorganic compounds through the skin was studied by Lang and Kunze.[43] They applied solutions of lead acetate, lead orthoarsenate, lead oleate, and tetraethyl lead to the bare skin of a number of rats and measured the amount of lead in the kidney as an index of absorption. In all cases, the amount of lead in the kidney was greater than in controls; tetraethyl lead produced the greatest difference. If the skin was traumatized before the lead solutions were applied, there was a threefold or fourfold increase in renal lead concentration. It is likely that absorption through unabraded skin by various lead compounds is primarily dependent on their relative lipid solubilities.

Because of the difficulty, particularly in tetraethyl-lead-contaminated atmospheres, in attempting to separate cutaneous exposure from respiratory exposure, the role of cutaneous lead absorption in relation to blood lead levels is still unclear.

10.3 DISTRIBUTION

When a single dose of lead enters the body, it is distributed initially in accordance with the rate of delivery of blood to the various organs and systems. The material is then redistributed to organs and systems in proportion to their respective affinities for lead. When daily ingestion is consistent for an extended period, a nearly steady state is achieved with respect to intercompartmental distribution. The steady-state condition will be disturbed, however, whenever short-term high levels of lead intake are superimposed on such a long-term ingestion pattern.

10.3.1 Human Studies

Autopsy data have shown that lead becomes localized and accumulates in bone. This accumulation begins in fetal life,[44,45] since lead is readily transferred across the placenta. The concentration of lead in the blood of newborn children is similar to that of their mothers,[46,47] and the distribution of lead in fetal tissue is similar to that of adults.[45]

The total content of lead in the body may exceed 200 mg in men aged 60 to 70 years, but in women it is somewhat lower. Calculations by several investigators[48] show that in nonoccupationally exposed adults 94 to 95 percent of the total body burden is in the bones.[44,49,50] These reports not only reaffirm the affinity of bone for lead, but also provide evidence that the concentrations of lead in bones increase at least until middle age (50 to 60 years old).[48,51] On the contrary, neither soft tissues nor blood show age-related changes in lead concentration after age 20.[52,53] Thus, it seems that the skeleton is a repository that reflects the long-term accumulative exposure to lead, whereas body fluids and soft tissues equilibrate rather rapidly and reflect only recent exposures.

The concentration of lead in the blood is utilized as an index of exposure to assess conditions considered to represent a risk to health.[54] Plasma lead concentrations have been shown to be constant at 2 to 3 μg/dl over a range of 10 to 150 μg/dl whole blood.[55] Recent studies have indicated that lead is bound primarily to erythrocyte protein, chiefly hemoglobin, rather than to stroma.[56]

Rabinowitz used a stable lead isotope tracer (^{204}Pb) to determine the rate of equilibration of blood lead with input.[21] He found that in human subjects with a constant daily oral intake of ^{204}Pb, a virtually constant concentration was measured in blood after about 110 days. When lead was removed from the diet, the concentration in the blood disappeared with a half time of approximately 19 days. Tola et al.[57] reported that the concentration of lead in the blood rises fairly rapidly to a new steady-state level in about 60 days when men are introduced into an occupational lead-exposure situation, a situation similar to that cited for exposure chambers in clinical studies.[58]

Although the body burden of lead increases throughout life,[48,50,52] measurements of specific organs and systems show that the total burden is divided between two general pools within the body. The major portion of the lead is contained in bone. This pool is clearly highly accumulative and, as a consequence, lead accumulates here rather consistently and continuously. The second pool comprises other organs and systems and accumulates much less. The levels of lead in this pool tend to stabilize early in adult life and thereafter demonstrate a turnover rate sufficient to prevent accumulation.

Since the organs and systems that contain the relatively mobile lead pool are of greater toxicological significance, it is clear that a mobilizable or exchangeable lead burden is a more important concept than is total body burden. In this connection, chelatable urinary lead has been shown to provide an index of the mobile portion of the total lead burden.[59,60] Among adults in the general population there are no age-related differences in concentrations of lead in whole blood or in blood serum. Thus, in a general way, the blood lead level is an indicator of the concentration of lead in soft tissues, and the changes in blood lead levels observed when there are changes in exposure levels probably reflect similar changes in some organs and soft tissues.

Lead exposure causes the development of nuclear inclusion bodies containing lead in both man[61-63] and animals. Although they seem to occur most frequently in the kidney, they have been found in other organs as well.

The concentrations of lead in deciduous teeth are of interest because tooth analysis represents a noninvasive technique and because teeth provide a record of long-term lead exposure. The dentine is particularly useful in this respect because it is laid down from the time of eruption to the time the tooth is shed. Concentrations of lead in dentine are reported to be considerably lower in suburban school children than in children residing in areas of high lead exposure.[64]

Primarily because of the relative ease with which hair can be collected, there have been some studies of the possible use of hair lead as an index of exposure. These studies have not been sufficient, however, to provide significant information on the relationship between hair lead concentrations and the amount of exposure. Rabinowitz et al.[65] fed labeled lead (^{204}Pb) to 3 subjects daily for approximately 100 days. Levels of isotope in the blood were immediately elevated but in facial hair there was a much more gradual response, with a delay of approximately 35 days.

10.3.2 **Animal Studies**

Administration of a single dose of lead to rats produces high initial concentrations of lead in soft tissues which then fall rapidly as the result of excretion and transfer to bone.[66] The distribution characteristics of lead within the animals' bodies were found to be independent of the dose over a wide range. Castellino and Aloj[67] described the rate constants for the elimination of lead from various tissues in rats following a single dose. Lead was eliminated from bone much more slowly than from other tissues. Bolanowska et al.[68] reported that the rate of elimination of a single dose of lead from rats became slower with time, reflecting progressively decreasing mobility of the residual body burden.

Goldstein et al.[69] sacrificed 21-day-old rats 24 hr after intravenous injection of various single doses (1, 50, 200 μg) of labeled lead (^{210}Pb) and found that the concentration of radioactivity in the brain was directly proportional to the blood radioactivity. Studies of O'Tuama et al.[70] indicate, however, that this process may not be one of simple passive diffusion of lead into neural tissue. These latter investigators sacrificed guinea pigs at 5, 60, and 240 min. after the intravenous injection of tracer doses of lead (^{210}Pb) in both subacutely intoxicated (155 mg $PbCO_3$/day for 5 days) and control animals. Radioactivity in barrier tissues (such as choroid plexus and meninges) rose rapidly, with concentrations ranging to more than ten times the simultaneous brain radioactivity. Subsequently, there was a fall in the barrier tissue levels, but brain levels remained fairly constant and low throughout the period of the study. The apparent discrepancies may be explained in large part by the differences in the ages of the animals as well as other factors, including species differences, time of sacrifice, or a more complex mechanism of distribution.

Rather striking age-related differences in the distribution and retention of lead in rats have been observed.[71] Elimination of a single tracer dose of ^{203}Pb from the whole body, blood, and kidney occurred more rapidly in adult than in suckling rats. In sucklings there was a slight increase with time in the ^{203}Pb content of the brain following administration of the dose, whereas the content in other soft tissues decreased with time.

The intracellular distribution of lead has been studied in rat tissue, mainly by cell-fractionation techniques.[72,73] Membranes, especially mitochondria, have shown an affinity for lead. Little lead is found in lysosomes,[73] however, in contrast with the intracellular distribution of many other metals, e.g., mercury, copper, and iron.

There are few studies of target organs in which lead concentrations at the site of the effect have been specifically determined. In particular, direct assessment of lead level in bone marrow is difficult to carry out, although the sensitivity of the hematopoietic system to lead has been extensively investigated. Formation of nuclear inclusion bodies is observed in rats with renal lead concentrations of about 10 mg/kg (wet weight) of kidney.[74] Other effects of lead were found to occur only at higher levels of organ concentration. Death in cattle is associated with lead levels of about 50 mg/kg (wet weight) of kidney cortex.[75]

The concept of estimating the lowest level of metal accumulation that results in adverse effects in a target organ has not been well explored in the case of lead. This is in contrast with cadmium, for which estimates have been made of the minimum concentrations in the kidney cortex at which evidence of renal damage appears.[76]

10.4 ELIMINATION

The major portion of excreted lead appears in urine and feces, but lesser quantities are removed via sweat, hair, nails, and exfoliated skin.

10.4.1 Human Studies

Fecal excretion represents the major route of organic and inorganic lead elimination. The rate of fecal lead excretion has been reported to be 100 times the rate of elimination in urine;[77,78] however, most of the lead in feces represents metal that has not been absorbed.

Rabinowitz et al.[79] studied the excretion of tracer lead from the blood of a nonoccupationally exposed human subject. Urinary and fecal excretion of ^{204}Pb from the blood amounted to 38 and 8 μg/day, accounting for 76 and 16 percent, respectively, of the measured recovery. The crude estimation of lead in hair, nails, and sweat yielded a value of 4 μg (8 percent). The urinary excretion was similar to the average daily lead excretion of 31 μg/day reported by Teisinger and Srbova.[80] Booker et al.[81] administered lead(^{212}Pb) intravenously to 2 human subjects and then recovered 4.4 percent of the dose in urine during the first 24 hr. Lead was not detected in feces. During the second 24 hr, about 1.5 percent was measured in both urine and feces. Thus, gastrointestinal transit appears to play an important role in the rate of excretion in feces of systemically administered lead.

The clearance of lead from the blood of man into urine was found by Vostal[82] to be proportional to the rate of creatinine excretion, with urinary lead extrapolating to zero at zero creatinine.

The characteristics of urinary lead excretion may be affected by the chemical form of lead. Whereas all of the lead in urine of subjects with normal exposure can be precipitated by the addition of agents such as oxalate, phosphate, or carbonate, only one-third to two-thirds of the lead in the urine of lead workers is available for precipitation.[83] These results suggest the presence of a stable lead complex in the urine of exposed workers.

Lead is excreted in sweat as well as urine. Schiels[84] reported that ingestion of lead acetate increased the lead concentration of sweat twofold to fourfold. Schroeder and Nason[85] found the concentration of lead in the sweat of lead-intoxicated subjects to be similar to that in urine.

Since studies of net lead retention suggest that, at low level exposures, higher intakes are followed by higher rates of excretions[5-7,17,59] and that lead excretion appears to be disproportionately low in cases of high-level exposure, there is not yet a predictable relationship between increases in lead exposure and in lead excretion.

10.4.2 Animal Studies

The relative importance of lead excretion from blood into urine and feces varies with the species tested. Within 12 hr, 7.4 percent of an intravenous dose appeared in the feces of rats compared with a recovery of 2.3 percent from urine.[86] In sheep, also, fecal elimination is more rapid than urinary excretion of lead.[87] In contrast, urinary excretion was reported to be two times greater than fecal excretion in baboons.[89]

There are indications that most of the translocated lead (from blood to intestine) is derived from bile. Of the 7.5 percent of an intravenous dose of lead acetate excreted by sheep in the feces within 6 days, 81 percent originated in bile.[87] Similar results were obtained from rats.[86,89] Although species differences in gastrointestinal transit time and the presence of a gallbladder can explain differences in the rate of appearance of a single injected dose of lead in the feces, these factors do not account for differences in the relative amounts of steady-state lead elimination in urine and feces.

Measurements of lead clearance into the urine of animals, like those in man, require an accurate measurement of the free lead concentration in blood. Since most of the lead in blood is bound to red cells and to plasma proteins, this measurement is virtually impossible.

Whether the renal tubule takes an active part in lead excretion is open to question. More recently, it has been found that the renal tubule cell transports lead into the urine,[90] perhaps because of the presence of lead-binding ligands in the tubular cell. These observations demonstrate that the renal excretion of lead involves more than filtration of the metal at the glomerulus. It is likely that the responses of secretory and reabsorptive processes to increased circulating lead levels contribute to the relative constancy of urinary excretion in humans[5-7] and in laboratory animals[74] that were exposed to high doses of lead.

10.5 ALKYL LEAD METABOLISM

The toxic effects caused by tetraethyl lead and tetramethyl lead are not produced by the tetraalkyl compounds themselves, but rather by the trialkyl derivatives formed by dealkylation in the liver.[86,91] Tetraethyl lead is converted primarily to triethyl lead and partly to inorganic lead.[92] Triethyl lead concentrates in organs and disappears very slowly. Even after several days, there is no significant reduction. Tetramethyl lead is much less toxic than tetraethyl lead, probably because it is dealkylated to the trialkyl toxic form much more slowly than is tetraethyl lead.[93]

Since both these compounds have toxic and biochemical effects unlike those of inorganic lead, the biochemical indices used in assessing inorganic lead exposure would not be expected to have the same significance in assessing exposure to organic lead. Indeed, in cases of severe, acute tetraethyl lead poisoning, urinary coproporphyrins and ALA excretion are not usually elevated, and free erythrocyte porphyrins are only moderately and inconsistently elevated.[94,95] These biochemical tests are therefore of little use in short-term exposure situations. In long-term exposure situations, however, it is possible that some of them may be useful. Indeed, Robinson[96] has shown that in industrial workers exposed to tetraethyl lead, urinary excretion of ALA is increased, but not to the same degree as in workers exposed to inorganic lead who have similar levels of total urinary lead excretion (organic plus inorganic). Bolanowska et al.[97] demonstrated that in three fatal cases of tetraethyl lead poisoning the ratio of inorganic lead to triethyl lead ranged from 67:1 to 18:1 in the urine. This ratio did not reflect the ratio of inorganic to triethyl lead in tissues, including the brain where the ratio was approximately 1:1.

10.6 METABOLIC CONSIDERATIONS IN THE IDENTIFICATION OF SUSCEPTIBLE SUBGROUPS IN THE POPULATION

The discussion on the metabolism of lead has up to now only tangentially specified differences in metabolism between children and adults (Section 10.2.2). There are, however, physiological dynamics of child growth and development that have significant implications for the increased risk of children exposed to lead. There are, as well, differences between children and adults in the intake, desposition, etc., of lead.

Metabolic, physical, and other differences between children and adults that must be considered include: (1) children have considerably less surface area than adults, e.g., a 2-year-old child has one-third the surface area of an adult; this parameter is not known to be directly related to the risks associated with lead exposure;[98] (2) there is greater lead intake by infants on a per-unit-body-weight basis, which is probably related to greater caloric and water requirements; (3) there is greater intake in children as well as net absorption (Section 10.2.2), resulting from greater net respiratory intake along with greater net absorption and retention from the gastrointestinal tract; (4) the rapid growth rate of children may reduce the margin of safety against a variety of stresses, including iron deficiency, etc.; (5) dietary habits of children in some respects[99-101] are quite different from those of adults; normal hand-to-mouth activity such as thumb sucking occurs as well as the habit of retrieving dirt-contaminated foodstuffs; (6) in children the likelihood of protein, calcium, and iron deficiency is so great relative to intake that a negative balance in these factors may exist; (7) in very young children metabolic pathways[99-101] are known to be incompletely developed, e.g., the blood-brain barrier in newborns; and (8) partitioning of lead in the bones of children is different from that of adults.[100,101] Only 60 to 65 percent of the lead body burden is in the bones of children. More important is the possible lability of the bone fraction of lead in children, particularly in the case of coexisting calcium deficiency. Rosen and Wexler[102] find an increasing resorption of lead in rat bone organ culture when calcium in the medium is reduced.

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11. BIOLOGICAL EFFECTS OF LEAD EXPOSURE

11.1 INTRODUCTION

As noted in Chapter 2, air-quality criteria documents present the scientific knowledge of the relationship between pollutant concentrations and their adverse effects on public health and the environment. This chapter addresses the important human health and biological effects of lead exposure.

Section 11.2 treats the biochemical and pathological basis of the various health effects of lead, centering on enzymology and the subcellular and cellular aspects of lead effects on the various organ systems. Section 11.3 presents a brief overview of clinical lead poisoning — that is, lead exposure leading to a constellation of adverse health effects that require medical intervention. It is not the purpose of that subsection to suggest that airborne lead invariably induces clinical lead poisoning as defined in this document; rather, it seeks to state the consequences to health, both immediate and long term, of the upper range of exposure to this pollutant regardless of its source and to state this in a discrete portion of the document.

The respective sections on organ systems have been ordered according to the degree of known vulnerability to lead of each system. The emphasis is not only on the three systems classically considered most sensitive — hematopoietic, nervous, and renal — but also on reproduction and development in view of lead's effects on the fetus, and, therefore, on pregnant women. Some effects can be considered to involve a number of organ systems, and the available data on multisystemic effects are presented in the final subsection.

Subdividing the chapter on the health effects of lead into organ systems was done for the purpose of easier discussion. It must be kept in mind that, in reality, all systems function in delicate concert to preserve the physiological integrity of the whole organism. Furthermore, all systems are interdependent in the organism, so that not only are effects in a critical organ transmitted to other systems but also low-level effects, which may be construed as less important in a single specific system, contribute to the cumulative or additive adverse effects of minimal biological response in a number of systems.

11.2 CELLULAR AND SUBCELLULAR EFFECTS OF LEAD

11.2.1 Effects on Enzymes

In general, the effects of lead on enzymes may be manifested in several ways. Lead, in common with a number of other metals, has an affinity for a number of complexing groups resident in the structure of many biomolecular entities, such as imidazole nitrogen, the cysteine sulfhydryl group, and the ε-amino group of lysine. An effect may be imparted, therefore, by binding-site competition with the native ion, by perturbation of the structural integrity of enzymes, or by the impediment of substrate-enzyme binding.

Cellular damage caused by lead may also permit the movement of enzymes into the circulatory system, with a resulting elevation of enzyme activity in, for instance, plasma.

The effects of lead on enzymes and enzyme systems have been studied in both animals and exposed human subjects and *in vitro* and *in vivo*. Clearly, many of these studies in the literature are of marginal relevance to this particular document and are briefly summarized for reference reading without evaluation.

On the other hand, a number of other enzyme systems are of such distinct relevance that they are better elaborated in the specific sections on organ effects. For example, the enzymology relating to the heme biosynthetic pathway is discussed in Section 11.4.

Enzymes that have been shown to be affected by lead in animal studies are presented in Table 11-1, and results of studies on enzymes in humans are presented in Table 11-2.

11.2.2 Organellar and Cellular Effects

It is of interest to duscuss briefly the subcellular distribution of lead before further comment is made on cellular effects.

TABLE 11-1. ENZYMES AFFECTED BY LEAD IN ANIMAL STUDIES

Enzyme	Effect on activity	Reference
Lipoamide dehydrogenase	Inhibited	1
DNAase	Enhanced	2.3
Serum glutamic oxaloacetic transaminase (SGOT)	Enhanced and transitory	4-7
Serum glutamic pyruvic transaminase (SGPT)	Enhanced and transitory	4-7
Serum alkaline phosphatase (AP)	Lowered	7
Erythrocyte and liver AP	Variable	7.8
Acid phosphatase	Quenched or markedly inhibited	7,9,10
Catalase	Variable	11-13
Cholinesterase	Markedly inhibited	5.6.14
α-Mannosidase	Increased	15
β-Acetyl glucosaminadase	Increased	15
Succinate oxidase	Decreased	16
Cytochrome *c* reductase	Decreased	16
Glutamate dehydrogenase	Decreased	16
Cytochrome oxidase	Decreased	16
Rat brain adenyl cyclase	Decreased	17
β-Glucuronidase	Elevated	18
β-Galactosidase	Elevated	18

TABLE 11-2. ENZYMES AFFECTED BY LEAD IN HUMAN STUDIES

Enzyme	Effect on activity	Reference
SGOT and SGPT	Enhanced	19-21
SGOT and SGPT	No effect	22
Serum alkaline phosphatase	Reduced	23
Acid phosphatase	No effect	24.25
Aldolase	Enhanced	26
Cholinesterase	Inhibited	27-29
Glutlathione reductase	Enhanced	30
Glucose-6-phosphate dehydrogenase	Inhibited	30

Castellino and Aloj,[31] using ^{210}Pb, found a decrease in radioactivity over a 24- to 72-hr time interval in the nuclear fraction and an increase of ^{210}Pb in the mitochondria fraction using liver. Over the same time interval, an increase in radioactivity occurred in the kidney in both nuclear and mitochondrial fractions, and there was a decrease in microsomes. Mitochondrial binding was particularly strong.

Similarly, Barltrop et al.[32] measured ^{203}Pb in heart, liver, kidney, and spleen following intraperitoneal (i.p.) administration. Their results indicated that most of the lead accumulated in the mitochondria.

A detailed study of the rat kidney by Goyer et al.[33] showed that over a protracted period the cell nucleus accumulated the highest proportion of lead.

Under lead challenge, a cellular reaction typical of a variety of animal species is the formation of intranuclear inclusion bodies, the early experimental history of which has been reviewed by Goyer and Moore.[34] The presence of considerable lead in these bodies has been verified by X-ray microanalyses;[35] ultrastructural studies show that this entity consists of a rather dense core encapsulated by a fibrillary envelope.

The work of Goyer,[33,36] indicates that these inclusion bodies are a complex of lead and protein, the protein moiety having characteristics of the residual acidic fractions of proteins in normal nuclei. The morphological integrity of these inclusion bodies collapses on treatment *in vitro* with metal chelants such as EDTA. A role for the inclusion body as a cellular protective mechanism during transcellular lead transport has been postulated.[36]

How the localization of lead in nuclear inclusions relates to nuclear function has not been established; however Choie and Richter[37] have shown that i.p.-administered lead enhances DNA synthesis and proliferation of renal tubular cells. The effects of lead on cell division are detailed in Section 11.2.4. Disaggregation occurs in the ribosome in the presence of lead.[1,38]

Animal experiments and human studies, mainly centered on cellular energetics and morphological aberrations, have shown mitochondria to be highly sensitive to lead. Teras and Kakhn[39] showed decreased respiratory rates in mitochondria of rabbit tissue under chronic lead challenge using a-ketoglutarate, succinate, and pyruvate as substrates. Phosphorylation was also retarded.

A marked sensitivity of the pyruvate-NAD reductase system in kidney mitochondria of lead-intoxicated rats is suggested by the work of Goyer and Krall,[40] who note impairment of pyruvate-dependent respiration using ADP/O ratios and respiratory control rates (RCR's) as indices. Succinate-mediated respiration in lead-intoxicated rats, however, was not different from that of control animals.

Rhyne and Goyer[41] state that their observations of decreased oxygen uptake rates for both State III and IV in succinate-dependent respiration in mitochondria of the kidney from lead-intoxicated animals may be evidence of decreased succino-oxidase enzyme, which would also be consistent with decreased mitochondrial protein.

Walton[42] reported an accumulation of lead in granules produced in isolated rat-liver mitochondria following incubation in media containing lead, with the lower end of the range of the free lead level employed approaching that found in lead-poisoning victims. It was noted that lead-rich granules, unlike those obtained with calcium, were not dispersed after treatment with dinitrophenol. This finding would indicate that lead removal after deposition is difficult. The above observations and other studies prompt the suggestion that lead effects are twofold: (1) energy diversion to the active accumulation of lead would prevent ATP synthesis and the preservation of ionic gradients in the membrane; and (2) the chemical action of lead would promote ATP hydrolysis, and lead would complex with essential SH groups of mitochondrial enzymes and interact with anions. The net result is the inability of cells to maintain themselves structurally and metabolically.

Recent studies by Kimmel et al.[43] on the chronic long-term exposure of rats to lead showed that subcellular effects of lead on the renal system were apparent when comparatively low levels of lead (5, 50, and 250 ppm in drinking water) were administered prenatally and up to 9 months of age postnatally. Light microscopy showed karyomegaly and cytomegaly at all dose levels. Electron microscopic examination indicated swollen mitochondria, numerous dense lysosomes, and intranuclear inclusion bodies at 50 and 250 ppm. Furthermore, considerable alteration in the activity of heme biosynthetic pathway enzymes (δ-ALA synthetase and ferrochelatase) was observed at 50 and 250 ppm. The blood lead values for the different dose regimens ranged from 5 μg/dl for control animals and 10 μg/dl for the 5 ppm group to 25 μg/dl for the 50 ppm group and 70 μg/dl for the 250 ppm animals.

Cramer et al.[44] studied renal biopsy tissue of five workers having varying periods of exposure to lead. Although the typical lead-induced nuclear inclusion bodies were found only in those with short exposure, all subjects showed mitochondrial changes. Mitochondria in the tubular lining cells showed swelling and distortion of cristae, with some of the mitochondria transected by cristae.

An important comment here relates to the indications of impaired mitochondrial function of erythroid tissue in humans that can be assessed by changes in levels of free erythrocyte (actually zinc erythrocyte) protoporphyrin (FEP) and urinary coproporphyrin. The discussion of the hematopoietic system in Section 11.4 includes treatment of this relationship.

In addition, the intramitochondrial stages of heme synthesis have been suggested to have an intermediary role in introcellular metabolism and are probably required for the continued transfer of iron from extracellular sites to normoblasts of reticulocytes.[45,46]

The *in vivo* effects of lead on erythrocytes in humans include: accumulation of lead, increased osmotic resistance, increased mechanical fragility, increased glucose consumption, increased potassium loss in incubation, decreased sodium- and potassium-dependent ATPase activity in membrane fragments, and elevation in the number of immature red cells.[47-49] A more detailed discussion of erythrocyte-lead relationships is given in the hematopoietic section.

Jandl and coworkers[50] demonstrated that the uptake of ^{59}Fe by human reticulocytes was almost completely inhibited by 5 x 10^{-4} M lead and that its incorporation into hemoglobin was almost entirely prevented. This resulted in an elevated level of iron in the erythrocyte membrane.

The major cellular pathology of concern in the kidney with reference to lead is that of the proximal convoluted tubular cells. Initial atrophy of the epithelial cells in this region is followed by cell regeneration along with an increase in intertubular connective tissue, basement membrane thickening, and round cell proliferation. Tubular cell mitochondria swell and degenerate, as noted before, and glomeruli show increased cellularity.[51] Tubule cells also show the presence of nuclear inclusion bodies, a description of which has been made *(vide supra)*.

In the suckling-rat model for lead encephalopathy employed by Pentschew and Garro[52,53] in which lead exposure of the pups is via milk from mothers fed lead carbonate, epithelial cell dysfunction in brain capillaries is evidenced by abnormal permeability to Trypan Blue and Thorotrast (colloidal thorium dioxide). The lesion possibly centers on interference with an energy-regulating mechanism peculiar to its barrier function.

Schlaepfer[54] has suggested that the neuropathy of lead poisoning may be caused by initial damage to the supporting cells of the nervous system. Dorsal root ganglion capsular cells show a proliferation and accumulation of dense bodies in their cytoplasm that microscopically possess the features of a heavy metal. It is possible that the metabolism of the capsular cells is impaired, which then causes the degeneration of associated neurons and axons and has a deleterious effect on the ganglion cells. A common site for intoxication in both the capsular cells and the Schwann cells of the peripheral nervous system has been suggested to account for both axonal degeneration and segmental demyelination[55] because these two cells have a common embryological origin.[56]

Moore et al.,[57] in a study of the cardiac effects of lead in the drinking water of rats, found that when rats were exposed to lead in drinking water at a level similar to levels previously found in Glasgow, Scotland, there was a significant inhibition of cardiac ferrochelatase and δ-aminolevulinic acid dehydratase that was maximal after 6 months. Moreover, electron microscopy revealed marked changes in myocardium and myocardial mitochondria.

11.2.3 **Effects of Lead on Chromosomes**

The examination of chromosomes for damage is technically difficult. The evaluation of the relevance of many studies can therefore be equally difficult. Because the appropriate separation of chromosomes into two chromatids and equal redistribution of chromatids during cell division are necessary for the reproduction of stable new cells for the maintenance of healthy tissue, the implications of injury to chromosomal material are profound, and interruption of the processes involved can be serious. Incorrect division of cells by the breakage of the chromatid, the migration of an inappropriate set of chromatids into either portion of a dividing cell, the abnormal reproduction of the complementary new chromatid to complete a viable chromosome in the new cell, and other deviations from the normal process can produce abnormal cells. Such chromosomal aberrations can, therefore, be responsible for the production of such serious consequences as genetic defects in offspring of the affected organism.

In the last few years, a number of reports have been published on the chromosomal effects of excessive exposure to lead in animals[3] and humans.[56-68] Although some of these reports have been essentially negative,[63-65] others have concluded that there is a definite increase in the number of chromatid and chromosome changes in subjects who are occupationally exposed to lead.[56-62] Thus, the literature is controversial in regard to chromosomal abnormalities induced by exposure to lead.

O'Riordan and Evans[63] did not find any significant increase in chromosomal damage in male workers exposed to lead oxide fumes in a shipbreaking yard. These shipbreakers had blood lead values ranging from 40 to over 120 μg/dl. Schmid et al.[64] found no evidence of increased chromosomal aberrations in peripheral lymphocytes, studied both *in vivo* and *in vitro*, in lead manufacturing workers. Furthermore, Bauchinger et al.[65] found no abnormalities in the chromosomes of policemen with elevated blood lead levels (20 to 30 percent above the mean for the control group).

An increase in chromosomal aberrations in people occupationally exposed to lead whose mean blood lead values were 38 to 75 μg/dl has been reported, however, by Forni and Secchi[58] and by Schwanitz et al.[56] Moreover, Deknudt et al.[60] reported chromosomal damage in a group of 14 male workers with signs of lead poisoning. Although the workers were exposed to zinc and cadmium as well as lead, the authors concluded that lead should be considered responsible for the aberrations. The study by Forni and Secchi[58] showed that the rates of chromatid changes were higher in 65 workers with preclinical and clinical signs of lead poisoning but were not significantly raised for workers with past poisoning. Forni et al.[62] also examined 11 subjects before and during initial occupational exposure to lead. The increase in the rate of abnormal chromatid metaphases (the separation of the pair of chromatids during normal cell division) was doubled after 1 month of exposure, was further increased after 2 months, remained in this stage up to 7 months, and then decreased. The fact that most alterations were of the chromatid type, that is, occurring in cell culture after DNA synthesis, indicates that these could be culture-produced aberrations and may not reflect a realistic *in vivo* situation. Also, a number of participants dropped out in the later stages of this study. Thus, the actual biological significance of these results is unknown.

In a recent report, Bauchinger et al.[66] found that chromosomal aberrations were significantly increased in a group of 24 male workers occupied in zinc electrolysis and exposed to zinc, lead, and cadmium. The workers had clearly elevated blood lead and blood cadmium levels in comparison with a control group. The authors emphasized the possibility of a synergistic effect of several metals on the chromosomes. They also pointed out the similarity between this group and the group studied by Deknudt et al.[60] in regard to exposure to a combination of lead, zinc, and cadmium. Referring to studies indicating the mutagenicity of cadmium, Bauchinger and his colleagues[66] were inclined to consider cadmium as being mainly responsible for aberrations; but Deknudt et al.[60] concluded that the abnormalities found were caused mainly by lead rather than by combinations of the three metals.

The question of whether chromosomal abnormalities occur in humans as a result of lead exposure, either alone or in combination with other pollutants, remains unanswered.[67] Furthermore, the human health significance of chromosomal abnormalities seen in lymphocyte cultures, a method used in some of the studies reported, is not yet known.[68] An assessment of the possible mutagenic effects of lead is further hampered by the technical difficulties that are inherent in the study of chromosomes.

11.2.4 **Carcinogenesis**

Lead salts have been shown to be at least co-carcinogenic in rats and mice.[69] The ultrastructure of experimentally lead-induced renal tumors in animals[70] is characterized by cellular and nuclear hypertrophy, the presence of numerous lysosomes and microbodies, and the absence of the infolding of basal plasma membranes that is normally seen in renal tubular lining cells. These tumor cells do not contain intranuclear inclusion bodies, and the lead content of the tumors is less than that in adjacent renal cortex. Renal adenomas and carcinomas were first observed in rats by Zollinger[71] in 1953 following long-term injections of lead phosphate. Later Kilham et al.[72] reported similar tumors in wild rats believed to have been exposed to lead fumes from burning refuse in a city dump. Lead-induced renal epithelial tumors have since been confirmed by a number of investigators.[70,72,73]

Swiss mice fed diets containing 0.1 percent basic lead acetate [$Pb(C_2H_3O_2)_2 \cdot 2Pb(OH)_2$] developed both benign and malignant renal tumors.[73] The same compound fed to rats at the 0.1 or 1 percent level similarly induced both benign and malignant kidney tumors,[70,74] and the incidence and size were related to the duration of lead feeding.[74] In male Sprague-Dawley rats fed a diet containing 1 percent basic lead acetate, Oyasu et al.[75] observed 2 cerebral gliomas and 13 kidney tumors in 17 animals. Van Esch and Kroes[73] reported renal changes but no neoplasms in 2 groups of 22 and 24 male hamsters fed, for up to 2 years, a standard laboratory diet containing 0.1 or 0.5 percent basic lead acetate.

Renal tumors were observed in rats fed diets containing 1 percent lead acetate [$Pb(C_2H_3O_2)_2 \cdot 3H_2O$],[76] and Goyer and Rhyne[77] reported that 60 to 80 percent of rats on a diet containing 1 percent lead acetate for more than 1 year developed renal adenomas or carcinomas with an increase in both size and incidence of carcinomas related to duration of exposure.

Subcutaneous or intraperitoneal injections of lead phosphate repeated over a period of several months also induced renal tumors. The total doses administered varied between 120 and 680 mg lead in the animals developing the tumors.[71,78]

In addition to renal neoplasms, tumors of the testes, the adrenal, thyroid, pituitary, and prostate glands, and the brain have been reported in Wistar rats fed lead acetate.[79]

The morphologic and co-carcinogenic effects of lead on the respiratory system were studied by Kobayashi and Okamoto.[80] Male and female golden hamsters were given a combination of 1 mg lead oxide and 1 mg benzo[*a*]pyrene intratracheally once weekly for 10 weeks; lung adenomas occurred in 11 of the 26 animals within 60 weeks. One adenocarcinoma of the lung was also observed. Any differences in frequency of occurrence between males and females were not mentioned. Such tumors did not occur in animals given the same dose of lead oxide or benzo[*a*]pyrene alone. It should be noted, however, that because lead compounds are only a small fraction of total particulates in air, there may be enough particulates even without lead for benzo[*a*]pyrene to be adsorbed so as to cause increased carcinogenicity.

Tetraethyl lead (TEL) [$Pb(C_2H_5)_4$] is an important, widely used, antiknock additive for motor fuels. Epstein and Mantel[81] reported that subcutaneous injection of 0.6 mg of TEL given as four equally divided doses to Swiss mice between birth and 21 days of age produced malignant lymphomas in 1 of 26 males and 5 of 41 females, compared with 1 of 39 males and none of 48 female control animals. The tumors were observed 36 to 51 weeks after the first injection in treated females.

No definite relationship between carcinogenicity and occupational exposure to lead has been established from human studies. In 1963, Dingwall-Fordyce and Lane[82] found only marginal evidence for any significant incidence of malignant diseases in their study of 425 persons who had been exposed to lead while working in a battery factory.

A study of the causes of mortality among lead smelter and lead battery workers in 1975 concluded that the incidence of malignant neoplasms, although somewhat greater than expected, was not statistically different from the incidence in the nonexposed population.[83] This seems to support the conclusion of a Working Group of the International Agency for Research on Cancer (IARC) that there is no evidence suggesting that exposure to lead salts causes cancer in humans.[69] The IARC view is supported by the fact that the comparable level of lead exposure that has been associated with malignant tumors in experiments on rodents is considerably higher than the toxic dose in humans.[69]

11.3 CLINICAL LEAD POISONING

Lead poisoning gives rise to recognized but nonspecific syndromes including acute encephalopathy, chronic encephalopathy, peripheral neuropathy, chronic nephropathy, and anemia.

Encephalopathy is the most severe acute clinical effect of lead poisoning and may emerge rather rapidly with the onset of intractable seizures followed by coma and cardiorespiratory arrest. When the outcome is fatal, death often occurs within 48 hours of the onset of encephalopathy.

In its fulminant form, development of encephalopathy occurs in less than a week. Periods of vomiting and apathy progressing to stupor are interspersed with periods of hyperirritability, poor memory, inability to concentrate, mental depression, persistent headache, and tremor. Several reports[85,86] indicate that children with acute encephalopathy may also incur acute renal injury (Fanconi syndrome), showing hyperaminoaciduria, glycosuria, and hyperphosphaturia.

Pediatric patients with lead poisoning frequently exhibit antisocial behavior and other behavioral disorders, including loss of motor skills and speech. They may also exhibit convulsive disorders; however, there are no clinical features that distinguish lead-induced convulsions from other seizure disorders. These findings are usually associated with blood lead levels in excess of 60 μg/dl and with increased density (in X-rays) at the end of long bones (lead lines). Because the latter indicates prolonged absorption of lead, this clinical picture is termed chronic encephalopathy. The above is very similar to the pattern seen with recurrent episodes of acute lead poisoning with or without acute encephalopathy, and the latter has been described by Byers and Lord[87] as well as Perlstein and Attala.[88] However, there may have been unrecognized episodes of acute encephalopathy at a previous time.

The peripheral neuropathy of lead poisoning centers on motor involvements with little effect on the sensory systems. This involvement may assume three clinical forms: (1) severe pain and tenderness in trunk and extremity muscles giving way to weakness and slow recovery; (2) the more common painless peripheral extensor weakness; and (3) neuropathic and myopathic features that are indistinguishable. This pattern is generally seen in workmen after 5 or more years of chronic exposure.

Patients with a history of one or more episodes of acute lead intoxication develop a nephropathy characterized by progressive and rather irreversible renal insufficiency. Progressive azotemia and sometimes hyperuricemia are noted. Late lead nephropathy generally is recognized at an irreversible stage.

The question of renal sequelae as a result of acute lead poisoning in children has been addressed in several reports. Henderson[89] noted that survivors of childhood lead poisoning in Australia demonstrate a very high frequency of chronic nephritis. Tepper,[90] however, did not confirm this in his Boston studies. Apparently, the length of exposure is of significance, as Tepper's subjects had incurred acute lead poisoning during preschool years whereas the Australian groups may have had exposure to lead for longer periods of time.

The anemia of lead poisoning is hypochromic and sometimes microcytic. It is also associated with shortened red cell life span, reticulocytosis, and the presence of basophilic-stippled cells. Further discussion of the hematopoietic effects is contained in Section 11.4.

Kline studied five patients having chronic lead poisoning.[91] At autopsy, evidence was found for lead encephalopathy in all, as well as evidence for chronic myocarditis. The latter was characterized by interstitial fibrosis with a serous exudate and relatively few inflammatory cells. From these observations, routine electrocardiographic studies and close scrutiny for evidence of myocardial damage was recommended by the author.[91]

Approximately 25 percent of young children who survive an attack of acute encephalopathy sustain severe permanent neurological sequelae.[92-94] Two studies[92,93] have indicated that a pediatric victim of acute encephalopathy has an almost 100 percent chance of severe permanent brain damage when returned to the same environment.

In its most severe form, acute lead encephalopathy may be followed by cortical atrophy, hydrocephalus *ex vacuo*, severe convulsive disorder, mental incompetence, and blindness. These results are becoming rare, however, and subtle neurological deficits and mental impairment are the more common outcomes.

Many children with documented prior attacks of symptomatic lead poisoning develop aggressive, hostile, and destructive behavior patterns. Although seizure disorder and behavior abnormalities may diminish during adolescence, mental incompetence is permanent.[2,87]

11.4 HEMATOLOGICAL EFFECTS OF LEAD

11.4.1 Anemia

Anemia of varying degree is a manifestation (often the earliest one) of clinical lead intoxication. Classically, the anemia is mildly hypochromic and sometimes microcytic. The anemia is associated with reticulocytosis (because of the shortened red cell survival) and the presence of basophilic stippling. Childhood lead poisoning is most frequently observed in children 1 to 6 years old and of lower socioeconomic status; in both these groups the prevalence of iron deficiency is quite high. A combination of iron deficiency and increased lead intake results in more severe anemia. Anemia, however, is also observed in children with increased lead intake who are not iron deficient. Six and Goyer[95] demonstrated that dietary iron deficiency in rats produced increased lead retention in liver, kidney, and bone with increased urinary δ-ALA excretion. Kaplan et al.[96] showed that the uptake of lead by erythrocytes in the presence of iron was decreased. These findings raised the possibility that iron-deficient children are more susceptible to the toxic effects of lead.

Although it is well known that anemia occurs in severe lead intoxication, the threshold blood lead level at which anemia occurs is not clearly established. In lead workers, Sakurai[97] could not demonstrate any difference in hemoglobin level up to a blood lead level of 50 μg/dl. Tola et al.[98] reported an effect of blood lead level on hemoglobin in a study of 33 workers at the beginning of their exposure to lead in an occupational setting and found that after 100 days of exposure, at the time when the average blood lead level had reached 50 μg/dl, the average hemoglobin level had decreased to 13.4 g/dl from the initial value of 14.4 g/dl ($p = <0.001$). Pueschel[99] observed a negative correlation between hemoglobin level and blood lead level in 40 children with blood lead levels ranging between 30 and 120 μg/dl. In this study, however, the ages of the individual children are not stated. A number of other studies also bear out the above observation.[100-102] It is known that in children aged 1 to 6 years there is a progressive physiological increase in hemoglobin level and that both iron deficiency and lead intoxication are most frequent in the youngest children.

The mechanism of anemia in lead poisoning appears to be a combination of decreased erythrocyte production as a result of the interference of lead with hemoglobin synthesis and increased destruction as a result of direct damage by lead to the red cell itself. The specific effects of lead at various steps in erythropoiesis are discussed below.

Approximately 90 percent of blood lead travels with the erythrocytes[103,104] as the lead is rapidly transferred from plasma to erythrocytes. Rosen et al.[100] have shown that plasma lead levels are a constant 2 to 3 μg/dl over a range of 10 to 150 μg/dl whole blood. McRoberts,[105] however, has shown that the plasma levels can fluctuate considerably and are associated with the appearance of symptoms in cases of occupational exposure. Kochen[104] has shown that erythrocytes primarily serve as a carrier for blood lead, with a binding capacity well above those lead levels associated with even very heavy exposure. It would appear, then, that the whole blood content of lead is relatively independent of hematocrit.

11.4.2 Effects of Lead on Erythrocyte Morphology and Survival

In lead poisoning, even in absence of iron deficiency, the erythrocytes are microcytic and hypochromic. Basophilic stippling is a frequent but inconstant feature of lead poisoning and has been employed as a method of monitoring workers in the lead industry. This test has the disadvantage of being nonspecific, as basophilic stippling may be observed in the erythrocytes of individuals with thalassemia trait and in several types of hemolytic anemia. Moreover, a good correlation between the amount of stippled erythrocytes and blood lead level has not been observed.[106] Recently Paglia and Valentine[107] have indicated that the basophilic stippling in lead poisoning results from the inhibition of the enzyme pyrimidine-5'-nucleotidase, which under normal conditions plays a prominent role in the cleavage of residual nucleotide chains that persist in the erythrocytes after extrusion of the nucleus. Decreased activity of this enzyme in persons with elevated blood lead levels is observed even when basophilic stippling is not morphologically evident, and it probably contributes to the shortening of the erythrocyte survival. It is known, in fact, that a severe chronic hemolysis is present in people who are genetically defective in pyrimidine-5'-nucleotidase.[108]

Osmotic fragility is decreased in lead poisoning. This is a common feature of many microcytic anemias, as it expresses the increased surface-to-volume ratio that results from the reduced hemoglobin content of individual erythrocytes. In lead poisoning, however, an increased osmotic resistance also results from a direct effect of lead on the erythrocyte membrane because increased osmotic resistance may be produced by lead *in vitro*.[109] Increased osmotic resistance has been proposed as a screening test for lead poisoning in children.[110] Other evidence of direct damage to the red cell membrane in lead poisoning is the markedly lowered activity of the sodium- and potassium-dependent membrane ATPase, which is indispensably coupled to active cation transport.[111] Shortening of erythrocyte survival has been shown by Hernberg et al.[112] using tritium-labeled difluorophosphonate and by Berk et al.[113] using detailed isotopic studies of a patient with severe acute lead poisoning. Leikin and Eng[114] observed shortened survival time in three out of seven children with lead poisoning and anemia. These studies indicated that hemolysis is not the exclusive mechanism of anemia and that diminished erythrocyte production plays an important role.

An additional factor is a large component of ineffective erythropoiesis. This was demonstrated by the detailed study of the patient of Berk et al.[113] in whom a marked increase of labeled stercobilin was observed after administration of labeled ^{14}C-glycine, a heme precursor. The presence of increased amounts of this heme catabolite in the urine demonstrates altered hemoglobin synthesis as a result of metabolic blockage or premature intramedullary destruction of red cell precursors, or both.

11.4.3 **Effect of Lead on Heme Synthesis**

The effects of lead on heme synthesis are quite well known both because of their prominence and because of the large number of studies in humans and experimental animals. The process of heme synthesis results in the formation of protoporphyrin IX, a complex molecule from small building blocks, glycine and succinate (as succinyl coenzyme A); it culminates with the insertion of iron at the center of the porphyrin ring. The initial and final steps of heme synthesis take place in the mitochondria, whereas most intermediate steps take place in the cytoplasm (Figure 11-1). Heme is formed in the mitochondria, and it is also an essential constituent of the cytochrome system located in the inner crest of the mitochondria themselves and is essential to cell respiration. Besides being a constituent of the cytochrome system and of several other heme proteins in the body, heme is the prosthetic group of

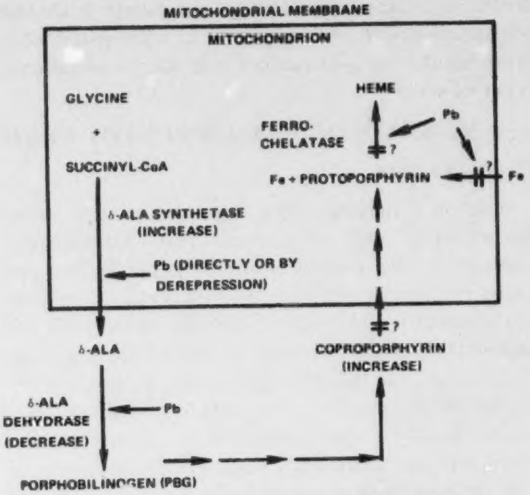

Figure 11-1. Lead effects on heme biosynthesis.

hemoglobin, the protein that transports oxygen from the respiratory system to every cell of the body. Hemoglobin represents 33 percent of the weight of red cells; so a normal 70-kg male with a red cell mass of 3000 ml has 1 kg of hemoglobin, approximately 35 g of which are heme. Therefore, with a red cell life span of 120 days, the daily production of heme for hematopoietic use is only around 300 mg.

Lead interferes with heme synthesis at several points. The two most important steps affected are the condensation of two molecules of δ-aminolevulinic acid (δ-ALA) to form the porphobilinogen ring (at the step catalyzed by the enzyme, δ-aminolevulinic acid dehydratase) and the insertion of iron into protoporphyrin IX (catalyzed by the enzyme, ferrochelatase). Other steps in the heme synthesis are affected by lead, such as δ-ALA-synthetase and coprogenase; these, however, may be affected indirectly through feedback derepression.

11.4.3.1 EFFECTS OF LEAD ON δ-AMINOLEVULINIC ACID DEHYDRATASE (δ-ALAD) AND δ-ALA EXCRETION

This enzyme is highly sensitive to the effect of lead and is directly inhibited by chelation of essential SH groups. The inhibition may be completely reversed by reactivation of the SH group *in vitro* by reducing compounds such as mercaptoethenol and dithiothreitol. The observation that δ-ALAD is inhibited by lead was first reported by Nakao et al.[115] and DeBruin[116] in 1968. Hernberg et al.[117] demonstrated that the logarithm of the activity of δ-ALAD was negatively correlated with blood lead level over a range from 5 μg/dl (the lowest value observed) to 95 μg/dl. In a detailed study of 25 healthy individuals with blood lead levels below 16 μg/dl, the same investigators found a similar correlation even in this lowest range.[118] These data suggested the direct inhibition by lead of δ-ALAD with no threshold effect because the enzyme was 50 percent inactivated at a blood lead level of 16 μg/dl and 90 percent inactivated at a blood lead level of 55 μg/dl. These observations have been confirmed by several other laboratories[119-123] for the general population, for industrial workers, and for children. In a study of 123 subjects, including 44 lead workers and 79 nonexposed persons (blood lead range of 4.5 to 9.3 μg/dl), Wada et al.[124] noticed a similar exponential negative correlation between blood lead and δ-ALAD. In a subsequent investigation,[125] the same author studied δ-ALAD in three groups: (1) 10 families (each including parents and one child) from a village far north of Tokyo with average blood lead of 8.3 μg/dl (range 5 to 10), (2) 10 families from central Tokyo with average blood lead of 12.8 μg/dl (range 9 to 17), and (3) 10 male workers with average blood lead of 26.5 μg/dl (range 14 to 36). In this study, a significant negative correlation between log ALAD and blood lead was found by combining groups 1, 2, and 3 or groups 1 and 2. In the first group, however, no such correlation could be demonstrated. Because this latter group comprised only 10 families from a small village, it is possible that failure to observe any relationship could be caused by the very narrow range of blood lead (5 to 10 μg/dl) and/or by genetic factors.

More recently Granick et al.[126] studied the ratio of δ-ALAD activity before and after reactivation with dithiothreitol in 65 children with blood lead levels between 20 and 90 μg/dl. By regression analysis, they estimated in this series that a ratio of reactivated/nonreactivated δ-ALAD of 1 (corresponding to no inhibition) would occur at a blood lead level of 15 μg/dl. Because of the wide range of variation and the small number of observations, however, the confidence limits of their estimate are quite large. On the other hand, Hernberg et al.[118] have shown a negative correlation in individuals with blood lead levels below 16 μg/dl, whereas the lowest blood lead level studied by Granick et al.[126] was 20 μg/dl. For these reasons, the observations of Granick et al.[126] do not contradict the evidence by Hernberg et al.[118] that δ-ALAD is already inhibited at the lowest levels of blood lead observed in humans in industrialized countries. Because the inhibition of this enzyme is a direct effect of lead in the blood, its correlation with blood lead is not surprising, and δ-ALAD activity may be used to estimate blood lead with a good degree of accuracy. The inhibition of δ-ALAD in erythrocytes reflects a similar effect of lead in body tissues, as shown by the studies of Secchi et al.[120] which demonstrated that, in 26 persons without industrial exposure to lead and with blood lead levels between 12 and 56 μg/dl, there was a clear correlation between erythrocyte and liver δ-ALAD and an expected negative correlation between blood lead and δ-ALAD in erythrocytes. Millar et al.[119] showed that when suckling rats were fed diets containing lead there was a significant and commensurate reduction of δ-ALAD activity not only in erythrocytes but also in liver and brain tissues. In a recent study by Roels et al.,[127] however, changes in tissue ALAD and free tissue protoporphyrin (FTP) were not found following postnatal lead administration in the rat. Lead was administered in the drinking water (0, 1, 10, 100 ppm) from parturition until day 21. In the offspring, an increase in Pb-B and a reduction in ALAD activity were found in the 10 and 100 ppm groups but no differences in hematocrit, hemoglobin, or FEP were observed. Lead storage in the kidney of the 100 ppm group was associated with a marked rise in kidney FTP but no differences were found in either ALAD or FTP in either liver, heart, or brain.

The inhibition of δ-ALAD is reflected in increased levels of its substrate, δ-ALA, in urine. Plasma δ-ALA has been shown[128] to be elevated in children with severe lead poisoning; however, because of the technical cumbersomeness of the techniques for measuring δ-ALA, few data are available on δ-ALA plasma levels at lower blood lead levels. On the other hand, urinary δ-ALA has been used extensively as an indicator of excessive exposure to lead, and it has even been suggested as a screening tool for lead poisoning.[129] Its use for this purpose has, however, been rejected because of the wide range of individual variability in daily excretion observed in some studies[130,131] Industrial use of this technique has been satisfactory, however.

Several studies have indicated that an excellent correlation exists between blood lead level and the logarithm of the level of urinary δ-ALA. Selander and Cramer[132] first described this relationship in 150 lead workers with blood lead ranging between 7 and 92 μg/dl. Their observations have been confirmed by other studies[123,124,133] in which a similar correlation was observed, in one case, even in the lower blood lead level range. Selander and Cramer[132] noticed that if lead workers were divided into two groups, those with blood lead levels below and above 40 μg/dl, two different linear correlation slopes could be derived, although with a lesser degree of correlation than the exponential relationship derived from the entire group. As cited in the NAS publication,[2] studies from Chisholm's laboratory showed a similar exponential correlation between blood lead level and urinary δ-ALA is 51 children aged 1 to 5 having blood lead levels ranging between 25 and 75 μg/dl. In 55 adolescents with blood lead levels ranging from 8 to 40 μg/dl, however, no clear correlation could be observed. It appears that apart from this last observation (which is restricted to adolescents, the great majority of whom had blood lead levels in a very narrow range: 14 to 24 μg/dl), all other studies reported show a clear exponential increase in δ-ALA urinary excretion with increase in blood lead. These observations parallel the reported exponential inhibition of the enzyme δ-ALAD and indicate that this is one of the earliest effects of lead on heme synthesis.

The urinary excretion of δ-ALA does not exceed the normal range (0.6 μg/dl) until the blood lead level reaches 40 μg/dl. The normal range, however, is derived from values obtained from individuals with blood lead levels up to 40 μg/dl. It is apparent that if δ-ALAD were inhibited by lead without any threshold of concentration and if δ-ALA were similarly affected, the definition of a normal range of δ-ALA excretion for individuals with a blood lead level less than 40 μg/dl would be ambiguous at best. Some of the discrepancies reported in the literature could in part reflect the larger variability of δ-ALA urinary excretion in comparison with erythrocyte δ-ALAD. In a detailed study by Alessio et al.[123] of 169 males with blood lead levels ranging from 5 to 150 μg/dl, the correlation between blood lead and δ-ALAD was much greater than with urinary δ-ALA. For these reasons and because of the uncertainty of defining a normal range, it is generally accepted that urinary δ-ALA becomes clearly abnormal at blood lead levels greater than 40 μg/dl. It has been postulated that there may be an excess of δ-ALAD activity, so that normal δ-ALA metabolism is still sustained by even 50-percent-inhibited enzyme at blood lead levels near 40 μg/dl. Above this value, however, the inhibition results in functional impairment and clear accumulation of δ-ALA, and increased urinary excretion may be observed. A recent study suggests that ALA may, in fact, be toxic systemically. The relative contributions from decreased utilization of ALA, as a result of ALAD inhibition and the derepression of ALA-synthetase, to urinary levels of ALA at blood levels at which excretion is significant cannot be determined at this time.

11.4.3.2 EFFECTS ON IRON INSERTION IN PROTOPORPHYRIN

The accumulation of protoporphyrin in the erythrocytes of humans with lead intoxication has been known since the 1930's.[135] Its use as an indicator of lead body burden, however, has been limited by the technical difficulties associated with the measurement of protoporphyrin by solvent partition and spectrophotometry. In 1972, the development of a simpler and more accurate technique, combining simplified extraction and fluorometry, made the measurement of protoporphyrin a widely used and accessible test.[136] As discussed in Chapter 9, several modifications of this technique have been developed, including an instrument that measures protoporphyrin by direct fluorescence in capillary blood samples without any extraction or manipulation of the blood sample.

Accumulation of protoporphyrin in the erythrocytes is the result of decreased efficiency of iron insertion into protoporphyrin, the final step in heme synthesis, which takes place inside the mitochondria. When this step is blocked by the effect of lead, large amounts of protoporphyrin without iron accumulate in the erythrocyte, occupying the available heme pockets in hemoglobin. Hence, protoporphyrin, rather than heme, is incorporated in the hemoglobin molecule where it remains throughout the erythrocyte life span (120 days).

The accumulation of protoporphyrin in lead poisoning is different from that observed in erythropoietic protoporphyria, a congenital disorder in which excess protoporphyrin is produced after heme synthesis is complete. In that case, the excess of protoporphyrin formed (as a result of a congenital defect in ferrochelatase) is attached to the surface of hemoglobin at a site that bridges the α- and β-chains of hemoglobin.[137,138] Because this type of bond to hemoglobin is very loose in erythropoietic protoporphyria, protoporphyrin diffuses through the plasma into the skin where it induces photosensitivity. In lead intoxication, on the other hand, the protoporphyrin in hemoglobin is bound more firmly to the heme pocket; hence, no diffusion into the plasma occurs and no photosensitivity is observed, despite extremely elevated erythrocyte protoporphyrin levels.

An additional important difference between the increased protoporphyrin level in the erythrocytes of persons with lead intoxication and erythropoietic protoporphyria is the fact that only in the former is the center of the protoporphyrin molecule occupied by zinc.[139] This difference is probably caused by the different affinity for zinc of protoporphyrin in the heme pocket. In lead intoxication, then, the largely prevalent species is zinc protoporphyrin, whereas in erythropoietic protoporphyria it is an unchelated protoporphyrin base. These two compounds differ in fluorometric spectra and the two conditions may be easily distinguished by spectrofluorometry.[140] Zinc protoporphyrin, attached in the heme pocket of hemoglobin, is also the prevalent species observed in iron deficiency, another condition in which an increased level of protoporphyrin is observed in the erythrocytes.

Accumulation of protoporphyrin in the erythrocytes in lead poisoning indicates a failure of the last step of heme synthesis. This could result either from a direct effect of lead on ferrochelatase itself or from an effect of lead on mitochondrial membranes of erythroid tissue in bone marrow, with consequent failure of iron transport. The latter mechanism would make iron, one of the two substrates of ferrochelatase, less available to enzyme action, with subsequent accumulation of the unutilized substrate, protoporphyrin IX.

Interference by lead with the mitochondrial transport of iron in the normoblast appears to be the most likely mechanism underlying the increased level protoporphyrin in the erythrocytes. Four facts support this statement: (1) iron accumulation within the erythrocyte is diminished by the presence of lead, whereas iron incorporation into heme is completely inhibited; (2) lead is deposited on the mitochondrial membrane, where it produces profound ultrastructural changes; (3) iron transport through the mitochondrial membrane is accomplished by both energy-dependent and energy-independent mechanisms that are impaired by lead;[141] and (4) in iron deficiency (when ferrochelatase activity is normal but iron is scarce) zinc protoporphyrin bound in the heme pocket is accumulated, whereas in erythropoietic protoporphyria (when iron is normal but ferrochelatase activity is decreased[142,143]) free protoporphyrin base loosely attached to the hemoglobin surface is formed.

Experimental evidence from animal studies and epidemiologic human studies, using intact mitochondria, have demonstrated the failure of iron incorporation into protoporphyrin in the presence of lead. These studies cannot clarify whether the effect of lead is exerted on the enzyme itself or on overall mitochondrial function. It is possible that mitochondrial transport of iron and ferrochelatase are both affected by lead.

The effect of lead on iron incorporation into protoporphyrin is not limited to the normoblast and/or to the hematopoietic system. Formation of the heme-containing protein, cytochrome P450, which is an integral part of the liver mixed-function oxidase system, may also be inhibited by lead.[144] Accumulation of protoporphyrin in the presence of lead has been shown to occur also in cultured cells of chick dorsal root ganglion, indicating that inhibition of heme synthesis takes place in the neural tissue as well.[145] These observations, and the fact that lead is known to disrupt mitochondrial structure and function, indicate that the lead effect on heme synthesis is exerted in all body cells, possibly with different dose/response curves holding for effects in different cell types. On the other hand, it must be noted that increased levels of protoporphyrin in the erythrocyte reflect an accumulation of substrate and therefore imply a functional alteration of mitochondrial function in the same way that the increased urinary excretion of urinary δ-ALA implies impairment. In other words, if a reserve activity of ferrochelatase exists, such as has been suggested for δ-ALAD, accumulation of protoporphyrin in the erythrocytes indicates that this has been hampered by the lead effect to the point that the substrate has accumulated. For these reasons, as well as for its implication of the impairment of mitochondrial function, accumulation of protoporphyrin has been taken to indicate physiological impairment relevant to human health.[146]

The elevation of erythrocyte protoporphyrin was shown to be exponentially correlated with blood lead level by Piomelli in a study of 90 children, covering the blood lead level range from 5 to 90 μg/dl.[147] In a later study of 1038 children, 568 of whom had blood lead levels greater than 40 μg/dl,[148] this correlation was confirmed, and it was clearly shown that all children with blood lead levels greater than 60 μg/dl had erythrocyte protoporphyrin greater than 250 μg/dl red blood cells (RBC's). Kamholtz et al.[149] and Sassa et al.[150] also showed a similar degree of correlation and indicated that a value of 140 μg FEP/dl RBC's would appear to be a more appropriate cut-off point for screening children for lead poisoning. This value, also suggested by McLaran et al.,[151] was accepted by Piomelli et al.,[152] who indicated that more than 70 percent of children with a blood lead level of 40 to

49 μg/dl have erythrocyte protoporphyrin in excess of this value. Several additional studies have confirmed the exponential correlation between blood lead and erythrocyte protoporphyrin in children[140,153-156] and in lead workers.[123,133,140,157,158]

Sassa et al.[150] demonstrated that a better correlation was observed between blood lead and erythrocyte protoporphyrin in children with a steady blood lead level. This finding suggested that a significant part of the scatter observed when blood lead is correlated to erythrocyte protoporphyrin on a random basis is the result of fluctuations of lead caused by day to day variation and experimental error.

Lamola et al.[140] demonstrated that the slope of elevation of erythrocyte protoporphyrin versus blood lead is steeper in children than in adult lead workers. This observation was confirmed by Roels et al.[159] who also demonstrated that the slope of elevation is similar in children and females. Reigert et al.[160] and Levi et al.[161] also demonstrated that an elevation of erythrocyte protoporphyrin can predict which children tend to increase their blood lead level and suggested that erythrocyte protoporphyrin is a more valuable indicator of childhood body burden of lead than the blood lead level itself. In adult workers, the elevation of erythrocyte protoporphyrin was shown to correlate with blood lead level, ALAD, ALA-U, and the duration of exposure to lead.[158] Chisholm et al.[162] suggested that in children erythrocyte porphyrin is a better indicator of overexposure to lead than blood lead. In addition to being elevated in lead intoxication, erythrocyte protoporphyrins may also be elevated in iron deficiency, but to a lesser degree. Several studies have indicated that erythrocyte protoporphyrin levels are an excellent indicator of the body iron store[164,165] and that these levels may also be used to discriminate between the microcytic anemia of iron deficiency (where they are elevated) and of thalassemia trait (where they are normal).[166-168]

These observations and the data collected on over 300,000 children screened by both erythrocyte protoporphyrin and blood lead in New York City were the basis for the statement by the Center for Disease Control (CDC) in which an elevation of erythrocyte protoporphyrin above 60 μg/dl of whole blood in the presence of a blood lead level above 30 μg/dl were indicated as cut-off points for the detection of childhood lead poisoning.[146]

Most studies on the relationship between erythrocyte protoporphyrin and blood lead have focused on persons (children or adult workers) with markedly elevated blood lead. Some studies, however, have shed light on the threshold level below which no effect is observed. In a study of children with blood lead levels over the range of 20 to 40 μg/dl, Sassa et al.[150] could not detect any threshold effect. Data from Roels et al.,[159] who studied 143 school children having blood lead levels ranging from 5 to 40 μg/dl, indicate a threshold effect at blood lead levels between 15 and 20 μg/dl. In a study by Piomelli et al.[169] of 1816 children aged 2 to 12 years (median age 4.7 years), the threshold for no effect of blood lead on erythrocyte protoporphyrin was estimated to be 15.5 μg/dl, using both probit analysis and segmental curve-fitting techniques.

Because an elevation of erythrocyte protoporphyrin is caused also by iron deficiency, it is important to take into consideration the iron state of the population under study in any evaluation of the relationship of this hematological index to lead exposure. No information is available with regard to the iron state of the population studied by Sassa et al.[150] In the Roels study,[159] similarly, no direct measurements of the iron status were obtained; however, the children studied ranged in age from 10 to 15 years, a group in which iron-deficiency anemia is uncommon. Moreover, the differences in blood lead were clearly related to living near or away from lead-emitting smelters. There is no reason to believe that the children who live near a smelter should have lower iron stores than the children who live in rural areas. Also, in the same study, it must be noted that the hematocrit of the children living in the rural area was slightly but significantly lower than the hematocrit of the children living near the smelter; therefore, if anything, the prevalence of any iron deficiency may have been greater in the rural children (with the lowest EP) than in the children living near the smelter (with the highest EP). These facts suggest that iron-deficiency anemia was not a factor in the elevation of erythrocyte protoporphyrin observed in this study, but that this EP increase was directly related to lead. In the study of Piomelli et al.,[169] an analysis of children aged 2 to 4 years versus children older than 4 years failed to show any difference in the EP/blood lead relationship. This indicates that iron-deficiency anemia, which is much more prevalent in the younger children, did not influence the EP response. Moreover, in the same study, the iron stores were measured in children with blood lead levels < 15 μg/dl and in children with blood lead levels of 15 to 28 μg/dl and no difference was observed. It appears, therefore, that the effect of the lead on EP, which is extremely well documented at the much higher blood lead level, occurs also in children with blood lead levels between 15 and 28 μg/dl.

These studies consistently demonstrate that an elevation of erythrocyte protoporphyrin, which indicates physiological impairment of heme synthesis and mitochondrial function, can be detected in children at a blood lead level that is well below levels normally encountered in screening procedures.

11.4.4 **Other Hematological Effects**

The effects of lead on δ-ALAD and on iron incorporation in protoporphyrin are the best known. In lead intoxication, however, other abnormalities of heme synthesis are observed. These include an increased activity of δ-ALA synthetase,[170] which may result by derepression, according to the scheme of negative feedback control proposed by Granick and Levene.[171] *In vivo* inhibition of coproporphyrinogen and uroporphyrinogen decarboxylases in rabbits[172] and inhibition of uroporphyrinogen I synthetase[173] have been reported. On the other hand, no accumulation of porphobilinogen has been observed in humans. An increased excretion of coproporphyrin in the urine of lead workers and children with lead poisoning is well known. Urinary coproporphyrin has been used extensively as a clinical indicator of lead poisoning. It is not known, however, whether this effect results from specific enzyme inhibition, from upstream accumulation of substrate secondary to inhibition of iron incorporation into protoporphyrin, or from both; or, alternatively, whether it is expressed as a disturbance of coproporphyrin transport through the mitochondrial membrane. Similarly, no data are available to establish a threshold blood lead level below which no excess coproporphyrin excretion in the urine takes place.

Besides the effect of lead on heme synthesis, hemoglobin synthesis may also be impaired because of inhibition by lead of the synthesis of globin (the protein moiety of hemoglobin). Kassenar et al.[174] showed impairment of globin synthesis. This work was confirmed by the results of Wada et al.[170] White and Harvey[175] showed a decreased synthesis of α chains compared to β-globin chains. Recently, Ali et al.[176] have shown an effect on globin synthesis *in vitro* on human reticulocytes at lead concentrations as low as 10^{-6} M, which corresponds to a blood lead level of 20 μg/dl.

11.4.5 **Summary of Effects of Lead on the Hematopoietic System**

A number of significant effects on the hematopoietic system in humans have been observed in lead poisoning. These effects are prominent in clinical lead poisoning, but they are still present to a lesser degree even in persons with lower body burdens of lead.

Anemia is a clinical fixture of lead intoxication. It results from both increased erythrocyte destruction and decreased hemoglobin synthesis. Erythrocytes are microcytic and have abnormal osmotic fragility as a result of direct effect of lead on the cell membrane, and show basiphilic stippling caused by the inhibition of pyrimidine-5'-nucleotidase. Erythrocyte survival time is shortened, and this results in hemolysis.

In children, a threshold level for anemia is about 40 μd Pb/dl, whereas the corresponding value for adults is about 50 μg Pb/dl.

Lead interferes with hemoglobin synthesis by inhibiting synthesis of the globin moiety and affecting several steps in the synthesis of the heme molecule. Most sensitive to lead in the heme synthetic pathway is the activity of the enzyme δ-ALAD, a zinc-activated enzyme that mediates the conversion of two molecules of δ-ALA into prophobilinogen. Inhibition of this enzyme results in increased plasma levels and urinary excretion of δ-ALA. Lead also inhibits the last step (incorporation of iron into protoporphyrin), which takes place in the mitochondria, probably by interference with the mitochondrial transport of iron and coproporphyrin. This effect results in the accumulation of coproporphyrin, which is excreted in the urine, and of protoporphyrin, which is retained in the erythrocytes, in the heme molecule. The overall effect of lead is a net decrease in heme synthesis, which in turn derepresses the enzyme involved in the first step of heme synthesis, δ-ALA synthetase.

Inhibition of δ-ALAD occurs at extremely low blood lead levels and has been shown to start at a blood lead level of 10 μg/dl. The resultant increased urinary δ-ALA excretion also starts at a very low blood lead level and becomes pronounced at a blood lead level ≥ 40 μg/dl.

The precise threshold for coproporphyrin excretion is not well established. It is probably similar to the threshold for δ-ALA, but it is less specific. An increase in erythrocyte protoporphyrin occurs at a threshold blood lead level of approximately 16 μg/dl in children. In adult females, the threshold is probably similar. In adult males, the threshold is probably slightly higher (20 to 25 μg/dl). The threshold for increase in δ-ALA synthetase is not established, but increases have been noticed at blood lead levels of ≥40 μg/dl.

Although doubt exists as to the health-effects significance of δ-ALAD inhibition, increased urinary δ-ALA excretion above 40 μg/dl is accepted as an effect probably reflecting physiological impairment.[2] Elevation of erythrocyte protoporphyrin has the same implication of physiological impairment *in vivo* as is found in urinary δ-ALA. Also, because elevation of erythrocytic protoporphyrin indicates impairment of mitochondrial function, it is considered of greater physiological relevance.[177] For these reasons, the consensus of clinicians who participated in the preparation of the statement in 1975 by CDC together with the American Academy of Pediatrics was that this finding should be used as an indicator of a significant and worrisome body burden of lead.

11.5 EFFECTS OF LEAD ON NEUROPHYSIOLOGY AND BEHAVIOR

Neurological and behavioral deficits have long been recognized as some of the more severe consequences of toxic exposure to lead.[178-182] What levels of lead exposure are necessary to produce specific deleterious neurological or behavioral effects and whether such effects are reversible, however, have been controversial medical issues extensively debated since the early 1900's. Much of the impetus for debate on the subject has been generated by progressively increasing medical concern over an evolving scientific literature that has consistently suggested, as more information is gained, that lead exposure levels previously accepted as harmless are actually sufficient to cause significant neurological or behavioral impairments. At present it is generally accepted that, at toxic, high levels of lead exposure that produce blood lead levels greater than 80 to 100 μg/dl, a person is at unacceptable risk for the occurrence of the clinical syndrome of fulminant lead encephalopathy. This syndrome includes neurological and other symptoms of such severity that immediate medical attention and, frequently, hospitalization is demanded in order to avoid irreversible neural damage or death. The risk involved is unacceptable because of the unpredictability of the symptoms observed at high blood lead levels. Based on the literature reviewed below, it now also appears that lower levels of lead exposure, yielding blood levels below 80 μg/dl, produce much less well-defined but medically significant neurobehavioral deficits in apparently asymptomatic adults and children, that is, in the absence of the neurological symptoms or other signs that typify acute lead intoxication requiring immediate clinical treatment.

The range of lead exposures necessary to produce the more subtle, subclinical neurobehavioral deficits is difficult to estimate with certainty and remains a matter of considerable controversy. There is some evidence reviewed below that suggests that such effects may occur at blood lead levels even as low as 30 to 40 μg/dl, whereas certain other negative findings suggest the lack of neurobehavioral effects at blood lead levels less than 80 μg/dl. In an effort to estimate the exposure levels necessary for manifestation of the full range of neurobehavioral effects of lead, the present discussion will critically review the literature dealing with the obviously toxic effects of high level lead exposures and with the more subtle neurobehavioral effects associated with lower exposure levels.

The relevant literature on the neurobehavioral effects of lead has been derived from studies of both humans and other mammalian species. Such effects have been indexed by means of a variety of approaches, including: (1) the assessment of structural neuropathology by classical histological and ultrastructural analyses of morphological damage; (2) the analysis of altered neurochemical parameters or processes by various biochemical assays; (3) the assessment of altered electrophysiological responses in both the central and peripheral nervous system; (4) the assessment of neurobehavioral effects both by neurological examinations and diverse types of behavioral testing methods; and (5) the assessment of alterations in neuropharmacological responses affecting many of the types of variables assessed by the other approaches. The effects of toxic, high-level exposures to lead have been well documented by most of these approaches. At lower-level exposures, however, the demonstration of lead effects by any of the above types of assessments has been complicated by several other methodological considerations that should be noted as a prelude to any critical review of the literature.

Data about lead exposure have been obtained via two basically different methods, epidemiological and experimental. Unfortunately, these methodological techniques are highly correlated with the species studied; that is, epidemiological techniques, with their unique problems, provide most human data, and experimental techniques are used to provide most nonhuman data. Although epidemiological studies have immediate environmental relevance at the human level, there are often difficult problems associated with interpretation of the findings. With epidemiological studies, the exact parameters of the most recent exposure level, the duration of any level of exposure, and the mode of intake usually cannot be entirely known. Similarly, any previous lead levels and exposure durations usually cannot be definitively established. It is also possible that other variables that were highly correlated with the presence of environmental lead, such as socioeconomic level, previous behavioral or neurological damage, etc., are responsible for the effects observed rather than lead exposure alone. There is a need for appropriate and sensitive measures of exposure effects, especially when testing for low-level effects for which less-than-dramatic neurobehavioral deficits can be expected. Nevertheless, the contribution of lead exposure to any neurobehavioral deficit(s) can be reasonably estimated with proper controls for many of the above extraneous factors.

Obviously such parameters as exposure levels and durations can be defined with much more precision in experimental studies carried out in the laboratory. Unfortunately, however, appropriate experimental designs are frequently lacking. In addition, environmental relevance of experimental laboratory data is limited by two major considerations. The most serious of these is the fact that nonhuman models are, of necessity, typically used for the establishment of dose-response curves, and it is well known that a large species difference exists in sensitivity to lead,[52] so that adequate nonhuman exposure models are difficult to devise. A second problem is that animal experiments frequently use doses of lead much higher than would be expected to occur in the environment. Besides the question of exposure levels, experimenters must attend to proper experimental controls for possibly reduced nutrition levels because of food palatability, if the delivery system is via food or water; effects of altered maternal behavior, if the delivery is via the mother's milk or the placenta, etc. Further, if central nervous system (CNS) alterations are noted, it is often difficult to separate damage caused by direct versus indirect effects on neural tissue. Again, despite the above difficulties, useful data on the neurobehavioral effects of lead have been obtained through animal studies, with potential implications for understanding human exposure effects.

Key variables that have emerged in determining the effects of lead on the nervous system include (1) the duration and intensity of exposure and (2) age at exposure. In reference to age at exposure, evidence exists for greater vulnerability of the developing nervous system in the young than of the fully matured nervous system in adults. Particular attention will, therefore, be accorded to the discussion of the neurobehavioral effects of lead in children as a special group at risk.

11.5.1 **Human Studies**

11.5.1.1 EFFECTS OF HIGH-LEVEL LEAD EXPOSURES

The severely deleterious effects of exposures to high levels of lead, especially for prolonged periods that produce overt signs of acute lead intoxication, are by now well documented in both adults and children. The most profound effects that occur in adults are referred to as the clinical syndrome of lead encephalopathy, described in detail by numerous investigators.[183-186] Early features of the syndrome that may develop within weeks of initial exposure include dullness, restlessness, irritability, poor attention span, headaches, muscular tremor, hallucinations, and loss of memory. These symptoms may progress to delirium, mania, convulsions, paralysis, coma, and death. The onset of such serious symptoms can often be quite abrupt, with convulsions, coma, and even death occurring very rapidly in patients that shortly before were apparently asymptomatic or exhibited much less severe symptoms of acute lead intoxication.[185,187] Symptoms of encephalopathy similar to those that occur in adults have been reported to occur in infants and young children,[85,90,185,188,189] with a markedly higher incidence of severe encephalopathic symptoms and deaths occurring in them than in adults. This may reflect the greater difficulty in recognizing early symptoms in young children that allows intoxication to proceed to a more severe level before treatment is initiated. In regard to the risk of death in children, the mortality rate for prechelation therapy period encephalopathy cases was approximately 65 percent.[190] Various authors have reported the following mortality rates for children experiencing lead encephalopathy since the inception of chelation therapy as the standard treatment approach: Ennis and Harrison,[191] 39 percent; Agerty,[192] 20 to 30 percent; McKhann and Vogt,[189] 24 percent; Mellins and Jenkins,[193] 24 percent; Levinson and Zeldes,[194] 19 percent; Tanis,[195] 18 percent; and Lewis et al.,[19] 5 percent. These data, as well as other data tabulated more recently,[2] indicate that once lead poisoning has progressed to the point of encephalopathy a life-threatening situation clearly exists and, even with medical intervention, is apt to result in a fatal outcome.

The morphological findings in cases of fatal lead encephalopathy vary.[197-199] On macroscopic examination the brains are often found to be edematous and congested. Microscopic findings of cerebral edema, altered capillaries (endothelial hypertrophy and hyperplasia), and a perivascular glial proliferation are often noted. Neuronal damage is variable and may be caused by anoxia. In some cases gross and microscopic changes are minimal.[198] The neuropathologic findings as reported are essentially the same for adults and children. Lead encephalopathy is considered by some to be primarily a vasculopathy, with the encephalopathy reflecting perturbed blood-brain barrier function;[198,199] that is, damage to neuronal elements may be secondary to lead effects on the vascular system. Evidence for such effects has been advanced by Pentschew.[198]

Pentschew[198] described neuropathology findings for 20 cases of acute lead encephalopathy in infants and young children. The most common finding was activation of intracerebral capillaries characterized by dilation of the capillaries with swelling of the endothelial cells. Diffuse astrocytic proliferation in the gray and white matter was also present. According to Pentschew, this proliferation is the earliest morphological response to an increase in permeability of the blood-brain barrier (dysoria).

Concurrent with the dysoric alterations were changes that Pentschew[198] attributed to hemodynamic disorders. These ischemic changes were manifested as cell necrosis, perineuronal incrustations, or neuronophagia (loss of neurons). The isocortex and the basal ganglia were areas of predilection for the ischemic changes. Pentschew concluded that the structural changes in infantile lead encephalopathy are a mixture of dysoric and hemodynamic parenchymal alterations. In the cerebellum, which in a restricted sense is the predilection area of damage, the changes are purely dysoric.

In addition to producing the above effects on the CNS, lead also clearly causes damage to peripheral nervous systems (PNS) of both man and animals at toxic, high exposure levels. The PNS changes involve predominantly the large myelinated motor fibers.[200] Pathologic changes in the PNS consist of segmental demyelination and in some fibers, axonal degeneration.[200] The lead effect appears to be in the Schwann cell, with concomitant disruption of the myelin membranes.[201] Remyelination has been observed in animal studies, suggesting either that the lead effect may be reversible or that not all of the Schwann cells are affected equally.[201] Reports of *pes cavus* deformities resulting from old peripheral neuropathies in humans,[202] however, suggest that lead-induced neuropathies of sufficient severity could result in permanent peripheral nerve damage. Morphologically, the neuropathy is characteristically detectable only after prolonged or high exposure to lead or both; data from experimental studies indicate that there are distinctly different sensitivities among different species.

Perhaps of even greater concern than the occurrence of fatalities are the neurological sequelae that occur in cases of severe or prolonged nonfatal episodes of lead encephalopathy that are qualitatively quite similar to those seen with many types of traumatic or infectious cerebral injury, with the occurrence of permanent sequelae being more common in children than in adults.[85,90,193] The most severe sequelae in children are cortical atrophy, hydrocephalus, convulsive seizures, and severe mental retardation.[85,90,193] More subtle sequelae also occur, such as impaired motor coordination, altered sensory perception, shortened attention span, and slowed learning. These latter effects have been reported in children with known high exposures to lead but without a history of the life-threatening forms of acute encephalopathy.[85,86,91,203] Of historical interest here in relation to the extremely slow progress in recognizing the full consequences of lead intoxication is the fact that, although many cases of childhood lead poisoning had been reported since the early 1900's,[180-182] it was several decades before the work of McKhann and Vogt[189] and Byers and Lord[85] called attention to the long-term irreversible neurobehavioral sequelae of acute lead intoxication.

Establishing precise threshold values for lead exposures necessary to produce the above acute intoxication symptoms or sequelae in humans is difficult in view of the usual inaccessability of extensive data on environmental lead levels contacted by the victim, the period of exposure, or the body burdens of lead existing prior to the manifestation of clinically significant symptoms. Nevertheless, enough information is available to allow for reasonable estimates to be made regarding the range of blood lead levels needed to produce acute encephalopathic symptoms or death. According to Kehoe[204-206] blood lead levels well in excess of 120 μg/dl are usually necessary to produce such deleterious irreversible effects for adults. Recurrent bouts of lead intoxication in the absence of acute encephalopathy may also lead to progressive mental deterioration. Other data exist, however,[187] that suggest that acute lead intoxication, including severe gastrointestinal symptoms or signs of encephalopathy or both, can occur in adults at lead levels somewhat less than 100 μg/dl; but ambiguities in these data make interpretation difficult.

The data on threshold levels for children indicate that lower blood lead levels have been associated with the occurrence of acute encephalopathy symptoms and death. Probably the most extensive compilation of information bearing on this point is a summarization[187] of data from the work of Chisholm[84,207] and Chisholm and Harrison.[90] That data compilation relates the occurrence of acute encephalopathy and death in children in Baltimore to blood lead levels determined by the Baltimore City Health Department (dithizone method) between 1930 and 1970. Elevated blood lead levels associated with asymptomatic cases or less severe signs of acute lead poisoning were also tabulated. Asymptomatic increased lead absorption was observed at blood levels ranging from 60 to 300 μg/dl (mean = 105 μg/dl). Acute lead poisoning symptoms, other than signs of encephalopathy, were observed from approximately 60 to 450 μg/dl (mean = 178 μg/dl). Signs of mild encephalopathy (hyperirritability, ataxia, convulsions) and severe encephalopathy (stupor, coma, convulsions repeated over a 24-hr period or longer) were associated with blood lead levels of approximately 90 to 700 or 800 μg/dl, respectively (means = 328 and 336 μg/dl, respectively). The distribution of blood lead levels associated with death (mean = 327 μg/dl) was essentially the same as for levels yielding either mild or severe encephalopathy. These data suggest that threshold blood lead values for death in children are essentially identical to those for acute encephalopathy and that such effects are manifested in children starting at blood lead levels of approximately 100 μg/dl. Other evidence reviewed below, however, suggests that the threshold for acute encephalopathy effects in the most highly susceptible children may, in some rare instances, be somewhat lower than the 100 μg/dl figure arrived at on the basis of the Baltimore data compilation presented above.

Occasionally appearing in the literature since the 1930's are scattered reports of acute lead encephalopathy or death occurring in children at what were formerly considered to be moderately elevated blood lead levels. For example, Cumings[185] listed references to studies on acute lead encephalopathy that appeared from 1938 to 1956. Several of the reports purportedly demonstrated acute encephalopathy in children at blood lead levels even down to 30 to 50 μg/dl. Detailed analyses of the articles referenced, however, indicate that the actual data reported in most did not clearly associate such low-level exposures to the occurrence of acute encephalopathy symptoms. Still, cases in at least some of the referenced articles and in other reports reviewed below suggest that acute encephalopathy occurred in a few children at blood lead levels below 100 μg/dl. Again, the ambiguities in these data regarding confirmation of lead exposure and elimination of alternative etiological factors make interpretation difficult. A further precaution has to do with the analytical methods themselves in terms of using good methods with skilled personnel.

In 1938, Gant[208] reported on five cases of acute lead encephalopathy in children under 2 years of age. Blood lead levels of 60 and 80 μg/dl, as well as 190, 240, and 320 μg/dl, were obtained for the different children upon first admission to the hospital. All five had convulsions. Smith[187] listed a 3-year-old female patient as having a blood lead level of 60 μg/dl at the time of acute lead intoxication from paint ingestion, followed by death attributed to plumbism 2 days after a 70 μg/dl reading was obtained during a period when only mild symptoms of lead poisoning were present. In 1956, Bradley et al.[209] reported that 19 children under 5 years old from a low income area of Baltimore were found to show CNS symptoms that included irritability, lethargy, or convulsions at blood lead levels below, as well as above, 100 μg/dl. Eight children who had been previously classified as asymptomatic and who had blood lead levels of 50 to 80 μg/dl were later hospitalized during the study[210] for treatment of acute lead encephalopathy; blood lead levels at the time of later hospitalization were not reported but were likely further elevated. Other data are reported[211] on 10 children from a low-income area of Providence, Rhode Island who were selected at 4 to 8 years of age for a follow-up investigation of possible long-term neurobehavioral deficits resulting from earlier acute encephalopathy episodes. Blood lead assays obtained at the time of the initial hospitalization of the children because of acute encephalopathy symptoms (4 out of 10 had convulsions, 8 out of 10 had ataxia, 7 out of 10 had drowsiness, and 6 out of 10 had irritability) yielded maximum blood lead values that averaged 88 ± S.D. 41 μg/dl. Because individual cases were not described, however, no clear association between particular lead intoxication symptoms and specific blood lead levels can be established. Overall, the above reports suggest that at least some children — perhaps especially inner-city children less than 4 years old — may be vulnerable to acute encephalopathy at blood lead levels of 80 to 100 μg/dl.

From the preceding discussion, it can be seen that severity of symptoms varies widely for different adults or children as a function of increasing blood lead levels. Some show irreversible CNS damage or death at levels less than 100 μg/dl, whereas others may not show any of the usual clinical signs of lead intoxication even at blood lead levels in the 100 to 200 μg/dl range. This difference may be caused (1) by individual biological variation in susceptibility to lead effects; (2) by changes in blood lead values from the time of initial damaging intoxication; (3) by better tolerance for a gradually accumulating lead burden; or (4) by any number of other interacting factors, such as nutritional state or inaccurate determinations of blood lead. In any case, in attempting to estimate exposure levels for adverse health effects of lead, the range of exposure levels yielding damaging effects to the most susceptible individuals needs to be emphasized rather than any average level at which such effects are seen. For adults, it would appear that the most susceptible individuals do not exhibit acute encephalopathy symptoms until blood lead levels of 100 μg/dl are reached or, more typically, are substantially exceeded. In regard to children, the majority of cases showing acute encephalopathic symptoms have blood lead levels of 100 μg/dl or more. For a very few cases, levels as low as 80 μg/dl have been reported.

11.5.1.2 EFFECTS OF LOW-LEVEL LEAD EXPOSURES

Also of great relevance for establishing safety limits for exposure to lead is the question of whether exposures lower than those producing symptoms of overt acute intoxication may exert more subtle, subclinical neurobehavioral effects in apparently asymptomatic adults or children. Attention has been focused in particular on whether exposures leading to blood lead levels in the 30 or 40 to 80 μg/dl range may lead to neurobehavioral deficits in the absence of any classical signs of lead encephalopathy. The literature on this subject is somewhat limited and controversial but still allows for certain statements to be made about the possible hazard of low to moderate lead exposure levels.

If such neurobehavioral deficits occurred in adults with great frequency, one might expect this to be reflected by higher rates of absences or reports of neurologically related symptoms among occupationally exposed lead workers. Some recent epidemiological studies have investigated possible relationships between moderately elevated blood lead levels and general health as indexed by records of sick absences that have been certified by physicians. No correlation between elevated blood lead levels and sickness rates or types of symptoms reported were found[212] for groups of workers in a lead storage battery factory from high-, medium-, and low-exposure areas versus control workers in nonexposure areas of the same plant. It should be noted, however, that mean blood lead levels for workers in the three exposure groups were 60, 50, and 42 μg/dl, respectively, compared with 45 μg/dl for the so-called nonexposure control group, rendering the conclusions of the report of dubious value. Similar negative findings were reported by Robinson[213] for tetraethyl-lead (TEL) workers having mean blood lead values of 43 μg/dl and daily urinary excretion of 0.089 mg of lead per liter urine over an 8- to 10-year period (3 to 4 times the rate for control group). Data on sickness rates were based on a retrospective study of records over a 20-year period. Absence or sickness reports, however, are probably not sensitive enough measures to detect subtle neurobehavioral symptoms.

Only a few studies have employed more sensitive psychometric and neurological testing procedures in an effort to demonstrate subclinical lead-induced neurobehavioral effects in adults. For example, Morgan and Repko[214] reported preliminary results of an extensive study of behavioral functions in 190 lead-exposed workers (mean blood lead level = 60.5 ± 17.0 μg/dl). In 68 percent of the subjects, blood lead was <80 μg/dl. The majority of the subjects were exposed between 5 and 20 years. The authors examined 36 nonindependent measures of general performance and obtained 44 measures of sensory, psychomotor, and psychological functions. Initial data analysis suggested that blood lead levels correlated with several reaction-time measures, and δ-ALAD changes correlated with effects on hand-eye coordination. This study, therefore, suggested that below a blood lead level of 80 μg/dl some behavioral changes did occur in adult workers. In addition, variability of performance increased with increasing blood lead level; however, only during period of high-demand performance did a worker's capacity clearly decrease as a result of lead exposure. Unfortunately, aspects of the Morgan and Repko work can be criticized because of methodological problems, including reported apparatus failures during testing of subjects. Also, findings analogous to those reported by Morgan and Repko were not obtained in a similar study[215] that found no differences between control and lead-exposed workers on a number of psychometric and other performance tests.

In addition to the above study[213] suggesting possible CNS dysfunctions, numerous investigations have provided electrophysiological data indicating that peripheral neuropathy symptoms are associated at times with blood lead values < 80 μg/dl. As reviewed by Seppäläinen,[216] reductions in nerve conduction velocities and electromyographic deficits have been observed in patients with known lead poisoning but without clinical neurological symptoms.[217-219] More recently, such peripheral nerve deficits were established by Seppäläinen[220] for lead workers whose blood lead levels were as low as 50 μg/dl and had never exceeded 70 μg/dl during their entire exposure period (mean = 4.6 years), as determined by regular monitoring. Similar results were obtained in a study by Melgaard et al.[221] on automobile mechanics exposed to TEL and other lead compounds in lubricating and high-pressure oils. Results of a multielemental analysis of the worker's blood for lead, chromium, copper, nickel, and manganese indicated a clear association between lead exposure and peripheral nerve damage. Half of the workers (10 of 20) had elevated blood lead levels (60 to 120 μg/dl) and showed definite electromyographic deficits. Mean blood lead level for the control group was 18.6 μg/dl. Melgaard et al.[221] reported additional results on associating lead exposures with polyneuropathy of unknown etiology in 10 cases from the general population. Another study reported recently by Araki et al.[222] provides further confirmation of the Seppäläinen[220] and Melgaard et al.[221] findings in that evidence for peripheral neuropathy effects were reported for lead-industry workers with blood lead values of 29 to 70 μg/dl. The very low blood lead levels, below 50 μg/dl, reported in some of the above studies, however, should probably be viewed with caution until further confirmatory data are reported on samples of larger size using well verified blood assay results.

In summary, the above studies, when taken together, appear to provide reasonably strong evidence that subclinical peripheral neuropathies occur in some adults having blood lead levels in the 50 to 70 μg/dl range. Furthermore, although it could be argued that substantially higher lead body burdens existing before the time of some of the studies were actually responsible for producing the neuropathies, it appears that in at least one case[220] blood levels always below 70 μg/dl were sufficient to cause peripheral nerve dysfunctions. That study by Seppäläinen[220] was also generally methodologically sound, having been well controlled for the possible effects of extraneous factors such as temperature differences at the nerve conduction velocity assessment sites. On the other hand, it should be noted that the data reported for control subjects were obtained at an earlier time (1971 to 1973) than data for the lead exposed subjects (early 1973); and no blood lead levels were reported for the control subjects. Still, when the Seppäläinen[220] results are viewed collectively with the data from other studies reviewed above, strong evidence appears to exist for peripheral neuropathies occurring in adults at blood lead levels of 50 to 70 μg/dl or, possibly, at even lower levels.

In addition to suspected neurobehavioral effects of relatively low-level lead exposures in adults, there is an increasing concern that low-level exposures producing blood lead levels of 40 to 80 μg/dl (or even less) in children may induce subtle neurological damage, especially to the very young developing CNS. This issue has attracted much attention and generated considerable controversy during the past decade. The evidence for and against the occurrence of significant neurobehavioral deficits at relatively low levels of lead exposure is, at this time, quite mixed and largely interpretable only after a thorough critical review of the methodologies employed in each of the various important studies on the subject.

One of the major approaches that has been employed is the retrospective analysis of lead levels existing in populations of apparently asymptomatic children that are then divided into nonexposed control and one or more lead-exposed experimental groups for comparisons of their performance in various neurological and psychometric tests. A few studies have been followed by subsequent further reëvaluation of the same children by the same investigators in an effort to assess whether indications of continuing neurobehavioral impairment still existed. Among the major studies that have employed this basic approach and that are widely cited in regard to this issue, those of de la Burde and Choate,[223,224] Perino and Ernhart,[225] Albert et al.,[226] and Landrigan et al.[227] suggest significant effects of asymptomatic, low-level lead exposure. In contrast, the studies of Kotok,[228] Lansdown et al.,[229] and McNeil et al.[230] report generally negative results. Two other studies, one by Landrigan et al.[231] and one by Kotok et al.,[232] although not reporting clearly statistically significant differences between moderately lead-exposed and control subjects, nevertheless report certain findings that are highly suggestive of a relationship between moderate lead exposure and cognitive impairment.

Among the several studies presenting evidence for CNS deficits being associated with blood levels of less than 80 μg/dl are the work of de la Burde et al.[223,224] and Perino and Ernhart.[225] De la Burde et al.[223] observed dysfunctions of the CNS, fine motor dysfunction, impaired concept formation, and altered behavioral profile in 70 preschool children exhibiting pica and elevated blood lead levels (in all cases above 30 μg/dl, mean = 59 μg/dl) in comparison to matched control subjects not engaging in pica. In a follow-up study on the same children (at 7 to 8 years old), de la Burde[224] reported further confirmation of continuing CNS impairment as assessed by a variety of psychological and neurological tests. This was despite the fact that many of the blood lead levels of the lead-exposed children had by then dropped significantly from the initial study. In general, the de la Burde et al.[223,224] studies appear to be methodologically sound, having many features that strengthen the case for the validity of their findings. For example, there were appreciable numbers of children (67 lead-exposed and 70 controls) whose blood lead values were obtained in preschool years and who were old enough (7 years) during the follow-up study to cooperate adequately for reliable psychological testing. The specific psychometric tests employed were well standardized and accepted as sensitive indicators of minimal brain damage, and the neurobehavioral evaluations were carried out blind, that is, without the evaluators knowing which were control or lead-exposed subjects.

The de la Burde[223,224] studies might be criticized on several points, none of which in the final analysis provide sufficient grounds for rejecting their validity. One difficulty is that blood lead values were not determined for control subjects in the initial study, but the lack of history of pica, as well as tooth lead analyses done later for the follow-up study, render it very improbable that appreciable numbers of lead-exposed subjects might have been wrongly assigned to the control group. Also, results indicating no measurable coproporphyrins in the urine of control subjects at the time of initial testing further help to confirm proper assignment of those children to the nonexposed control group. A second point of criticism addresses the probably inappropriate use of multiple chi-square statistical analyses in the manner employed to analyze the results of the study. Upon recomputation of the statistical significance of observed differences, by means of the more appropriate Fisher's exact probability test and accounting for the number of tests conducted, several measures originally reported to be statistically significant still turn out to be significant at $p < 0.05$ or lower. One last problem relates to ambiguities in subject selection that complicate interpretation of the full meaning of the results obtained. Because it is stated that the lead-exposed group included children with blood lead levels of 40 to 100 μg/dl, or of at least 30 μg/dl with "positive radiographic findings of lead lines in the long bones, metallic deposits in the intestines, or both," the reported deficits might be readily attributed to blood lead levels as low as 30 μg/dl. Other evidence,[101] however, suggests that such a simple interpretation may not be completely accurate. That is, the work of Betts et al.[101] indicates that lead lines are usually not seen unless blood levels exceed 60 μg/dl for most children at some time during exposure, although some (approximately 25 percent) may show lead lines at blood lead levels of 40 to 60 μg/dl. Virtually none have lead lines at levels below 40 μg/dl. In view of this, the de la Burde results probably can be most reasonably interpreted as demonstrating lasting neurobehavioral deficits at blood lead levels in excess of 50 to 60 μg/dl.

Similar conclusions are also warranted on the basis of results of the Perino and Ernhart study,[225] which demonstrated a relationship between neurobehavioral deficits and blood lead levels ranging from 40 to 70 μg/dl in a group of 80 inner-city preschool black children. One of the more interesting aspects of the findings is that the normal correlation of .50 between parent's intelligence and that of their offspring was found to be reduced to only .10 in the lead-exposed group, presumably because of the influence of another factor (lead) that interfered with the normal intellectual development of the lead-exposed children. Many of the methodological virtues of the de la Burde studies[223,224] were also present in the Perino and Ernhart[225] work, and blood lead determinations and statistical analyses appeared sound. About the only alternative explanation for these results might be differences in the educational backgrounds of the parents of the control subjects when compared with lead-exposed subjects, because parental education level was found to be significantly negatively related to the blood lead levels of the children participating in this study.

Parents of children in the lead-exposed group had significantly poorer educational backgrounds than the control group parents. The importance of this point lies in the fact that several other studies[233-235] have demonstrated that the higher the parental education level, the more rapid the development and the higher the intelligence quotients (I.Q.'s) of their children. It is nevertheless interesting that the de la Burde studies and the Perino and Ernhart work point to essentially the same conclusion, i.e., that neurobehavioral deficits occur at blood lead levels possibly as low as 40 μg/dl. Also, in both cases, the children studied were from inner-city, low-income areas.

Two other studies with positive findings had, for the most part, some serious methodological limitations. Albert et al.[226] found that asymptomatic children (5 to 15 years old) whose blood lead levels at an earlier age were elevated (>60 μg/dl) later had significantly more mental disorders and poorer school performance than a control group with lower lead levels in both blood and deciduous teeth. Unfortunately, however, no assay of the lead burden, in either blood or teeth, was done for about one-half of the children in the control group; and no significant effects were reported for children with lead levels < 60 μg/dl. Also, another major criticism is that some children in the control group had relatively high blood lead levels (>40 μg/dl). In another study, Landrigan et al.[227] found that asymptomatic, lead-exposed children living near a smelter scored significantly lower than matched controls on measures of performance I.Q. and finger-wrist tapping. The control children in this study were, however, not well matched by age or sex to the lead-exposed group, although it should be pointed out that results remained statistically significant even after appropriate adjustments were made for age differences.

In another relevant study, presented in a doctoral dissertation by Rummo,[211] significant neurobehavioral deficits were found (hyperactivity, lower scores on McCarthy scales of cognitive function, etc.) for children who had previously experienced high levels of lead exposure that had produced acute lead encephalopathy. Mean maximum blood lead levels for those children at the time of encephalopathy were 88 ± S.D. 40 μg/dl. Children with moderate degrees of blood lead elevation, however, were not significantly different from controls on any measure of cognitive functioning, psychomotor performance, or hyperactivity. On the other hand, if the data for performance on the McCarthy General Cognitive Index or several McCarthy Subscales are plotted graphically, as in Figures 11-2 and 11-3, then a rather interesting relationship between test performance and levels and duration of lead exposure becomes apparent.

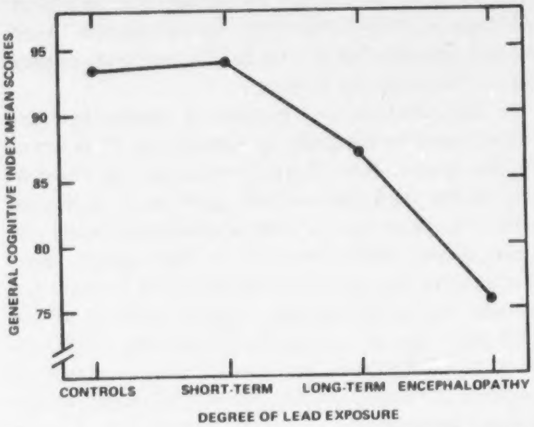

Figure 11-2. McCarthy General Cognitive Index scores as a function of degree of lead exposure.[211]

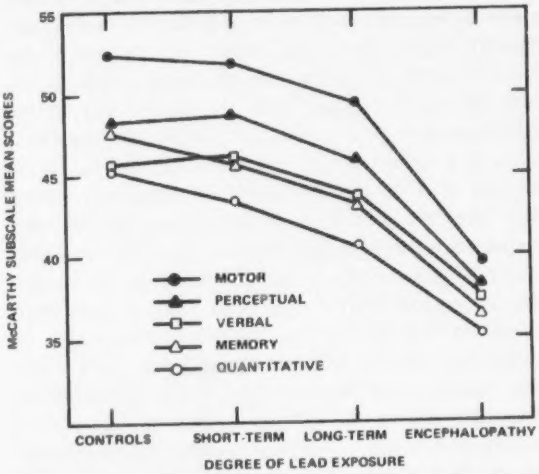

Figure 11-3. Scores on McCarthy Subscales as a function of degree of lead exposure.[211]

Although the scores for short-term moderate-exposure subjects are essentially the same as control values, an interesting aspect is that the scores for long-term moderate-exposure subjects consistently fall below those for control subjects and lie between the latter and the encephalopathy group scores. Thus, it would appear that long-term moderate lead exposure may, in fact, exert subtle neurobehavioral effects. This might be shown to be statistically significant by means of other types of analyses or if larger samples were assessed. It should be noted that (1) the maximum blood lead levels for the short-term and long-term exposure subjects were all >40

μg/dl (means = 61 ± S.D. 7 and 68 ± S.D. 13 μg/dl, respectively), whereas control subjects all had blood lead levels below 40 μg/dl (mean = 23 ± S.D. 8 μg/dl); and (2) the control and lead-exposed subjects were inner-city (Providence, Rhode Island) children well matched for socioeconomic background, parental education levels, incidence of pica, and other pertinent factors.

A somewhat similar pattern of results emerged from a more recent study by Kotok et al.[232] in which 36 Rochester, New York, control group children with blood lead levels <40 μg/dl were compared with 31 asymptomatic children having distinctly elevated blood lead levels (61 to 200 μg/dl). Both groups were well matched on important background factors, including, notably, their propensity to exhibit pica. Again, no clearly statistically significant ($p < .05$) differences between the two groups were found on a number of different tests of cognitive and sensory functions.

As indicated, however, by test results from the Kotok et al. study[232] presented in Table 11-3, the mean scores of the control-group children were consistently higher than those of the lead-exposed group for all six of the ability classes listed. Also, in one case the level of significance achieved borderline significance ($.10 > p > .05$), a pattern of results that hints at a trend existing toward lower ability levels for the lead group. The authors cautiously stated that "the data do not prove that these children have sustained no neurologic damage by lead" and that "later longitudinal testing may demonstrate cognitive or educational deficiencies." They also indicated that "evaluation of behavior, neurologic, or motor functioning was not carried out" and noted that "subtle cognitive and fine motor changes were demonstrated in an extensive and carefully controlled evaluation of asymptomatic children residing in the vicinity of an El Paso lead smelter."[227] They go on to imply that the earlier exposure to lead in infancy of the El Paso children and their longer period of exposure (mean = 6.6 years versus <3 years for the Rochester group) might account for the disparity in results between the two studies. Their results, on the other hand, plus the pattern seen in the Rummo[211] study, can be construed as evidence consistent with the findings of the de la Burde studies[223,224] and others reviewed above that report results linking low to moderate levels of lead exposure to significant behavioral impairments.

TABLE 11-3. COMPARISON OF TEST RESULTS IN LEAD AND CONTROL GROUPS[232]

Ability class	Group	Mean I.Q. ± S.D.	Significance
Social maturity	Lead	123.5 ± 22.7	$p > .10$
	Control	126.3 ± 17.7	
Spatial	Lead	92.0 ± 18.0	$.10 > p > .05$
	Control	100.8 ± 18.7	
Spoken vocabulary	Lead	91.7 ± 13.9	$p > .10$
	Control	92.9 ± 13.7	
Information-comprehension	Lead	94.5 ± 14.9	$p > .10$
	Control	96.3 ± 16.6	
Visual attention	Lead	89.7 ± 18.3	$p > .10$
	Control	93.3 ± 23.0	
Auditory memory	Lead	93.0 ± 24.0	$p > .10$
	Control	99.9 ± 32.0	

Other studies have produced mixed or negative results in attempts to determine whether a relationship exists between lead exposure and CNS deficits using various standardized psychometric techniques, neurologic examinations, and ratings by teachers, parents, or experimenters. For example, Kotok[228] reported earlier that developmental deficiencies (using the Denver Development Screening test, which is a somewhat insensitive measure of development) in a group of asymptomatic children having elevated lead levels (58 to 137 μg/dl) were identical to those in a control group similar in age, sex, race, environment, neonatal condition, and presence of pica, but whose blood lead levels were lower (20 to 55 μg/dl). The deficiencies could be correlated with inadequacies in the children's environment. Children in the lead-exposed group, however, had blood lead levels as high as 137 μg/dl, whereas some of the controls had blood lead levels as high as 55 μg/dl. Thus, the study was in effect a comparison of two groups with different degrees of elevation in lead exposure rather than one of lead-exposed versus nonexposed control children.

In several studies of children living in the vicinity of smelters or factories, significant neurobehavioral effects have typically not been found at moderate elevations of blood lead levels. For example, Lansdown et al.[229] found a relationship between blood lead level in children and the distance they lived from lead-processing facilities, but no relationship between blood lead level and mental functioning was found. Only a minority of the lead-exposed sample had blood lead levels over 40 μg/dl, however, one would not expect a striking relationship between mental functioning and lead levels below such a level.

In an extensive, generally thorough study, McNeil et al.[230] found that a sample of children living near a lead smelter in El Paso was comparable medically and psychologically to matched controls living elsewhere in the same city other than in the direct effects of lead (blood lead level, free erythrocyte protoporphyrin levels, and X-ray findings). Lead-exposed children in the group living near the smelter did, however, have significantly different personality test results, which were ascribed by the authors as being due to recent upheaval in the lives of the lead-exposed children who had been recently forced to move from the vicinity of the smelter. Considerable community unrest existed at the time of both the McNeil et al. study[230] and the work of Landrigan et al.[227] on the El Paso smelter area population, which grew out of circumstances associated with the discovery of the lead exposures and disposition of legal matters surrounding them. The impact of the extraneous unrest on both studies has tended to cloud interpretation of the true meaning of their respective results which in turn have become quite controversial. See Appendix E for more information. The personality test results of the McNeil et al.[230] study could nevertheless have been caused by the effects of lead on the exposed group. Also, it should be noted that a few suggestive trends toward statistical significance for certain interactions between lead and age of subjects ($p < .10$) were reported for some of the cognitive-function test measures.

Based on the above results, the authors of the Lansdown et al.[229] and the McNeil[230] papers concluded that no evidence was found for the occurrence of neurobehavioral effects at subclinical lead exposure levels in their studies. Perhaps that conclusion could be generalized to suggest that no significant CNS deficits typically occur as a result of subclinical, low to moderate lead exposures of children living in the vicinity of smelters or other lead-processing facilities. To the extent that those children may differ in significant ways from the inner-city children shown by de la Burde,[223,224] Perino and Ernhart,[225] and Albert[226] to have neurobehavioral impairments at blood lead levels as low as 40 to 50 μg/dl, ambiguous results from the smelter children are not necessarily contradictory to the better established findings of significant CNS effects for inner-city children. Furthermore, it should be noted that reports of peripheral neuropathies for both populations of children at low to moderate lead exposure levels, as described, may indicate that both groups are at significant risk for at least that type of neural tissue damage.

An additional approach, different from the basic strategy employed in the above studies, has been utilized in other studies in an effort to demonstrate that low or moderate blood lead levels cause significant neurobehavioral deficits. This approach consists of identifying populations of children with diagnosed neurobehavioral deficits of unknown etiology and assaying blood lead or making other assessments in order to link past lead exposures to the children's present neurobehavioral impairments. Thus, for example, efforts have been made to implicate moderate or low level lead exposures as a causative factor in at least some cases of hyperactivity of unknown etiology. The possibility that such low-level lead exposures induce hyperactivity has gained credence through the well documented[87,203] fact that hyperactivity is one of the frequent neurobehavioral sequelae observed in children who survive episodes of acute encephalopathy resulting from high-level lead exposures. The evidence for and against the hypothesis that low-level lead exposures produce hyperactivity has been accumulating at a rapid rate during the past few years and has generated considerable controversy on the subject. Only a few of the more salient findings are viewed below and in the section on animal studies (Section 11.5.2).

In a case-control study, David et al.[236] compared the incidence of elevated blood lead levels in five groups of children: (1) a pure hyperactive group with no apparent cause for hyperactivity; (2) a group of hyperactive children with a highly probable cause of hyperactivity, e.g., prematurity; (3) a group of hyperactive children with a possible cause; (4) a group of children who had recovered from lead poisoning; and (5) a nonhyperactive control group. Pure hyperactive children had statistically significantly higher blood lead levels (mean = 26.2 ± 8 μg/dl) than controls (mean = 22.2 ± 9.6 μg/dl), whereas children with a highly probable cause did not (mean = 22.9 ± 6.6 μg/dl). Similarly, the pure hyperactive children tended to excrete more lead than controls or probable cause hyperactives when given a single dose of penicillamine. Although the causal relationship between lead exposure and hyperactivity cannot be said to be proved by this study, the data of David et al.,[236] when placed with findings of hyperactivity in children known to have recovered from lead poisoning and numerous animal studies demonstrating alterations in motor activity following lead administrations, might be interpreted as supporting the hypothesis that a relationship between moderate lead exposure and altered motor activity exists.

On the other hand, several other points argue against acceptance of such a thesis at this time. For one thing, the David et al.[236] study itself and the author's conclusions can be questioned on several bases. In that study, for example, the closeness of the match of subjects in the five groups on variables other than age and sex is not clearly specified by the authors. Also, the interpretation of differences in blood lead levels in the 7-to-8-year-old children is fraught with numerous problems, not the least of which is the fact that such levels are probably not very accurate indices of long-past lead exposures that presumably occurred during preschool years. Many factors in the interim between presumed lead exposure and assay for lead could affect the results, including possible differentially higher incidences of pica in the hyperactive children than in control subjects. Klein et al.[237] have noted that pica may be part of certain behavioral syndromes that exist even in the absence of lead exposure, but that would predispose the affected child toward more lead ingestion by virtue of the habit's presence. Indeed, there is evidence that among mentally subnormal children whose mental deficiency can be definitely attributed to etiologies other than lead poisoning that there is both a high incidence of pica and moderately elevated blood lead.[238] Last, it should be noted that a number of other investigators,[211,227,229,230,239] who expressly looked for evidence of lead-induced hyperactivity as part of their screening for neurobehavioral deficits associated with blood lead levels as low as 40 μg/dl, failed to find any significant effects that support the thesis that low-level lead exposures induce hyperactivity. Thus, even though the hypothesis is intriguing and certainly worthy of further investigation, it cannot be stated at this time that sufficient evidence exists to establish hyperactivity as a neurobehavioral deficit clearly associated with low or moderate lead exposures.

In addition to the above data bearing on possible links between subclinical lead exposures and the induction of hyperactivity, certain recently reported data[240] provide evidence implicating increased heavy metal absorption, including lead uptake, in the etiology of learning disabilities. More specifically, children identified for other classification purposes as having learning disabilities were found to have significantly elevated levels of lead, as well as cadmium and some other metals, in their hair when compared with control children not classed as learning disabled. In fact, a discriminant function analysis yielded 98 percent accuracy in classifying children as normal or learning disabled based on a combined factor of cadmium, cobalt, manganese, chromium, and lithium levels. Lead was not included in this five-metal discriminant function, since its predictive value was well served by cobalt and cadmium because of a significant negative correlation between lead and cobalt ($r = .67; p < .01$) and a significant positive correlation between lead and cadmium ($r = + .53; p < .01$). Unfortunately for present purposes, no blood lead levels or possible past exposure histories were provided for the children in the above study.[240]

Other recent studies analogous in basic approach to that employed by David et al.[236] and Pihl and Parkes[240] have provided intriguing new information tending to link prenatal lead exposures to the later development of mental retardation. For example, Beattie et al.[241] identified 77 retarded children and 77 normal children matched on age, sex, and geography. The residence during the gestation of the subject was identified, and a first-flush morning sample of tap water was obtained from the residence. Of 64 matched pairs, no normal children were found to come from homes served with water containing high lead levels (>800 μg/liter), whereas 11 of the 64 retarded children came from homes served with water containing high lead levels. The authors conclude that pregnancy in a home with high lead in the water supply increases by a factor of 1.7 the risk of bearing a retarded child.

In a follow-up to the Beattie study, Moore et al.[242] obtained lead values from blood samples drawn during the second week of life and stored on filter paper. These samples had been obtained as part of a routine phenylketonuria screening study and were kept on file. Blood samples were available for 41 of the retarded and 36 of the normal children in the original study by Beattie. Blood lead concentrations in the retarded children were significantly higher than values measured in normal children. Mean blood lead for retardates was 1.23 ± 0.43 μMol/liter (25.5 ± 8.9 μg/dl) and for normals was 1.0 ± 0.38 μMol/liter (20.9 ± 7.9 μg/dl). The difference in lead concentrations were significant ($p = 0.0189$) by the Mann-Whitney test.

These two studies suggest that lead exposure to the fetus during the critical period of brain development may cause perturbations in brain organization that are expressed later in mental retardation syndromes, and they raise for careful scrutiny the risks of intrauterine exposure to lead. Insufficient information exists, however, to allow estimation of the levels of lead exposure of pregnant women that might cause those prenatal effects in the fetus that may result in later neurobehavioral impairments.

One last adverse effect of lead on neural function in children remains to be considered, and that is the possible induction of peripheral neuropathies by low-to-moderate lead exposures. It is generally accepted that lead-induced peripheral neuropathies, although frequently seen in adults after prolonged exposures, are extremely rare in children. Several articles[243-245] in the literature, however, do describe case histories that confirm the occurrence of lead-induced peripheral neuropathies, as indexed by electromyography, assessments of nerve conduction velocity, and observations of other overt neurological signs, such as tremor, wrist and foot drop, etc. Some of these frank neuropathic effects have been observed for several cases at blood lead levels of 60 to 80 μg/dl,[245] and in other cases peripheral neuropathy was associated with blood lead values of 30 μg/dl; however, in the latter cases, lead lines in long bones suggest probable past exposures leading to prior blood lead levels at least as high as 40 to 60 μg/dl and probably in excess of 60 μg/dl (based on the data of Betts et al.[101]). In each of the present case studies, there was reported some, if not complete, recovery of affected motor functions after treatment for lead poisoning. Further, it should be noted that a tentative association has been hypothesized between the existence of sickle cell disease and increased risk of peripheral neuropathy as a consequence of childhood lead exposure. Most of the cases reported involved inner-city black children, several with sickle cell trait. In summary, it appears that (1) evidence for frank peripheral neuropathy in children certainly exists; (2) such neuropathy can be associated rather well with blood lead levels at least as low as 60 μg/dl; and (3) evidence suggests that inner-city children with sickle cell disease may be at special risk.

Further evidence for lead-induced peripheral neuropathies in children is provided by the data of Landrigan et al.[231] derived from a study of children living in close proximity to a smelter in Idaho. The nerve conduction velocity results from this study are presented in Figure 11-4 in the form of a scatter diagram relating peroneal nerve conduction velocities (NCV) to blood lead levels in the children studied. No clearly pathologic conduction velocities were observed, although a statistically significant negative correlation was found between peroneal NCV and blood lead levels ($r = 0.38$, $p < .02$ by one-tailed t test). These results, therefore, provide evidence for significant slowing of nerve conduction velocity and, presumably, advancing peripheral neuropathy as a function of increased blood lead levels. The data do not allow for clear statements to be made regarding any threshold for a pathologic slowing of NCV.

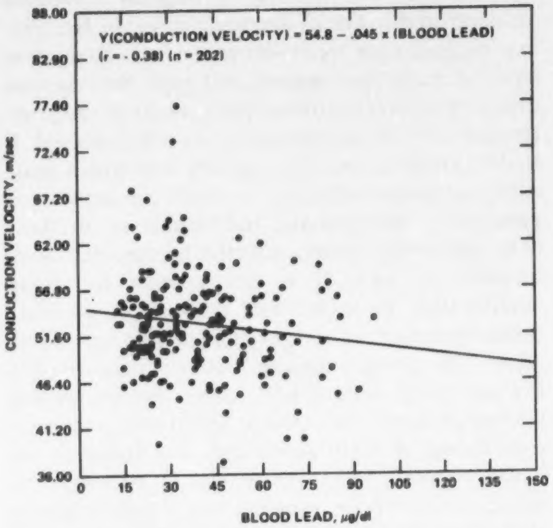

Figure 11-4. Peroneal nerve conduction velocity versus blood lead level, Idaho, 1974.[231]

11.5.1.3 SUMMARY AND CONCLUSIONS FOR HUMAN STUDIES

Rather than simply recapitulating in briefer form the findings reviewed above, an attempt will be made here to integrate information derived from the review and to focus on certain key issues concerning the impact of lead on human neurobehavioral functions. Among the key points to be addressed are: (1) the internal exposure levels, as indexed by blood lead levels, at which various adverse neurobehavioral effects occur; (2) the reversibility of such deleterious effects; and (3) the population(s) that appear to be most susceptible to neural damage.

Regarding the first issue, it would appear from data reviewed above that surprisingly low levels of blood lead can, at times, be associated with the most extreme effects of lead poisoning, including severe, irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathy symptoms or death or both. For most adults, such damage does not occur until blood lead levels well in excess of 120 μg/dl are reached. Evidence does exist, however, for the occurrence of acute encephalopathy and death in some adults at blood lead levels somewhat below 120 μg/dl. For children, the effective blood lead levels for producing encephalopathy or death are lower, typically starting at approximately 100 μg/dl. Again, however, good evidence exists for the occurrence of encephalopathy in some at lower levels, i.e., 80 to 100 μg/dl.

It should be emphasized that once encephalopathy occurs death is not at all an improbable outcome, regardless of the quality of medical treatment available at the time of any acute crisis. In fact, certain diagnostic or treatment procedures themselves tend to exacerbate matters and push the outcome toward fatality if the nature and severity of the problem are not fully recognized or are misdiagnosed. It is also crucial to note the rapidity with which acute encephalopathy symptoms or death can develop in apparently asymptomatic individuals or in those only apparently mildly affected by elevated body burdens of lead. It is not unusual for rapid deterioration to occur, with convulsions or coma suddenly appearing and progressing to death within 48 hr. This strongly suggests that even in apparently asymptomatic individuals rather severe neural damage probably does exist at high blood lead levels even though it is not yet overtly manifested in obvious encephalopathic symptoms. This tends to be borne out by studies showing that children having high blood lead levels (over 80 to 100 μg/dl), but not observed to manifest acute encephalopathy symptoms, are permanently, cognitively impaired, as are individuals who survive acute episodes of lead encephalopathy.

Other evidence tends to confirm that some type of neural damage does exist in asymptomatic children, and not necessarily only at very high levels of blood lead. The body of studies on low- or moderate-level lead effects on neurobehavioral functions, as summarized in Table 11-4, present overall a rather impressive array of data pointing to that conclusion. Several well-controlled studies have found effects that are clearly statistically significant, whereas others have found nonsignificant but borderline effects. Even some studies reporting generally nonsignificant findings at times contain data confirming statistically significant effects, which the authors attribute to various extraneous factors. Another way to look at the situation is to consider that elevated blood lead level is the single common factor extant in all of the groups showing significant behavioral deficits in the different studies. It should also be noted that, given the likely subtle nature of some of the behavioral or neural effects probable at low levels of lead exposure, one would not expect to find striking differences in every instance. The blood lead levels associated with neurobehavioral deficits in asymptomatic children appear to be in excess of 50 to 60 μg/dl. Great uncertainties remain, however, as to whether these exposure levels (observed blood lead levels) represent the levels that were responsible for the behavioral deficits observed. Monitoring of lead exposures in the subjects has in all cases been highly intermittent during the period of life preceding the behavioral assessment. In most cases, only one or two blood lead values are provided per subject.

11.5.2 **Animal Studies**

Pentschew and Garro[52] initially described an animal model of lead encephalopathy in which morphological changes occurred similar to those reported in children. Neonatal rats were exposed to lead by feeding mothers a diet containing 4 percent lead carbonate. The lead was then transmitted to the suckling young via the mothers' milk. Between 23 and 29 days of age, 90 percent of the animals developed paraplegia lasting no longer than 2 weeks. Eighty-five to 90 percent of the paraplegic animals died during this period.

Neuropathological examination of these animals revealed capillary activation, glial proliferation, areas of transudation, and spotty hemorrhages, primarily in the cerebellum and the striatum. The white matter of the cerebral hemispheres, especially the corpus collosum, was also involved, though to a lesser extent. Ischemic neuronal changes in focal distribution were rare and were localized in the cerebral cortex. Pentschew and Garro[52] concluded that the lead encephalopathy of the suckling rat was caused by a disorder in the permeability of the capillaries, resulting in dysoric encephalopathy. The suckling rat therefore differs from the human in that the latter shows a mixture of both dysoric and hemodynamic alterations. Further verification of the dysoric nature of lead encephalopathy in the suckling rat was provided by Lampert et al.,[53] who used either colloidal thorium dioxide (Thorotrast) or Trypan Blue, neither of which normally penetrates the blood-brain barrier. In suckling rats poisoned with 4 percent lead carbonate, however, both Thorotrast and Trypan Blue were found to penetrate the striatum and cerebellum.

Since the initial description by Pentschew and Garro,[52] lead encephalopathy in the rat has been replicated by Thomas et al.[246] Michaelson and Sauerhoff,[247] and Krigman and Hogan.[248]

Clasen et al.[249] reported lead encephalopathy in juvenile Rhesus monkeys exposed to 0.5 g of lead per day for 6 to 18 weeks. They reported morphological changes similar to those occurring in humans, which consisted of edematous changes in the cerebellar and subcortical white matter. Diffuse

TABLE 11-4. SUMMARY OF RESULTS OF HUMAN STUDIES ON NEUROBEHAVIORAL EFFECTS AT MODERATE BLOOD LEAD LEVELS

Reference	Population studied	N/group	Age at testing, yr	Blood lead, µg/dl	Psychometric tests employed	Summary of results (C= control; Pb= lead)[a]	Levels of significance[b]
De la Burde and Choate (1972)[223]	Inner city (Richmond, VA)	Control= 72	4	Not assayed[c]	Stanford-Binet IQ	C= 94 Pb= 89	$p < .05$
		Lead= 70	4	40-100[d]	Other measures	C >Pb on 3/4 tests	N.S.-$P < .01$
De la Burde and Choate (1974)[224]	Follow-up same subjects	Control= 67	7	See above[e]	WISC Full Scale IQ	C= 90 Pb= 87	$p < .01$
		Lead= 70	7	See above[e]	Neurologic exam	C better than Pb	$p < .01$
					Other measures	C >Pb on 9/10 tests	N.S.-$p < .001$
Perino and Ernhart (1974)[225]	Inner city (New York, NY)	Control= 50	3-6	10-30	McCarthy General Cognitive	C= 90 Pb= 80	$p < .01$
		Lead= 30	3-6	40-70	McCarthy Subscales	C>Pb on 5/5 scales	N.S.-$p < .01$
Pueschel et al. (1972)[99]	Inner city (Boston, MA)	Control= 56	?	<40	Stanford-Binet IQ	C= ? Pb= 86	—
		Lead= 56	?	>40	Neurologic exam	C better than Pb	$p < .001$
Landrigan et al. (1975)[227]	Smelter area (El Paso, TX)	Control= 46	3-15 ($\bar{x}$= 9.3)	<40	WISC Full Scale IQ[f]	C= 93 Pb= 87	N.S.
		Lead= 78	3-15 ($\bar{x}$= 8.3)	40-68	WPPSI Full Scale IQ[g]	C= 91 Pb= 86	N.S.
					WISC + WPPSI Combined	C= 93 Pb= 88	$p < .01$
					WISC + WPPI Subscales	C>Pb on 13/14 scales	N.S.-$p < .01$
					Neurologic testing	C >Pb on 4/4 tests	N.S.-$p < .001$
Rummo (1974)[211]	Inner city (Providence, RI)	Control Ss= 45	4-8 ($\bar{x}$= 5.8)	$\bar{x}$= 23± 8	McCarthy General Cognitive	C= 93; S= 94; L= 88; P= 77	N.S.-$p < .01$ (p vs C)
		Short Pb Ss= 15	4-8 ($\bar{x}$= 5.6)	$\bar{x}$= 61± 7	McCarthy Subscales	C+ S>L>P on 5/5 tests	N.S.-$p < .01$ (p vs C)
		Long Pb Ss= 20	4-8 ($\bar{x}$ = 5.6)	$\bar{x}$= 68± 13	Neurologic exam rating	C+ S L >P on ratings	N.S.
		Post enceph Pb= 10	4-8 ($\bar{x}$= 5.3)	$\bar{x}$= 88± 40	Objective neurologic tests	C+ S>L>P on 3/12 tests	N.S.-$p < .01$ (p vs C)
Kotok et al. (1977)[232]	Inner city (Rochester, NY)	Control= 36	1.9-5.6 ($\bar{x}$= 3.6)	11-40	IQE for six ability classes:	IQ Equivalent for each:	
		Lead= 31	1.7-5.4 ($\bar{x}$= 3.6)	61-200	Social maturity;	C= 126 Pb= 124	$p < .10$ for spatial
					Spatial relations; Spoken vocab; Info. comprehension; Visual attention; Auditory memory	C= 101 Pb= 92; C= 93 Pb= 92; C= 96 Pb= 95; C= 93 Pb= 90 C= 100 Pb= 93	$p > .10$ for all other ability classes
Kotok (1972)[228]	Inner city (New Haven, CT)	Control= 25	1.1-5.5 ($\bar{x}$= 2.7)	20-55	Denver Developmental Scale	C>Pb on 1/3 Subscales	N.S.
		Lead= 24	1.0-5.8 ($\bar{x}$= 2.8)	58-137			
Lansdown et al. (1974)[229]	Inner city (London, England)	Control= 172	6-16	<40	WISC	C= 100 Pb= 101-105	N.S.
		Lead= 43	6-16	40-60+	WAIS		
McNeil et al. (1975)[230]	Smelter area (El Paso, TX)	Control= 61-152	1.5-1.8(Mdn= 9)	<40	McCarthy General Cognitive	C= 82 Pb= 81	N.S.
		Lead= 23-161	1.5-1.8(Mdn= 9)	>40	WISC-WAIS Full Scale IQ	C= 89 Pb= 87	N.S.
					Oseretsky Motor Level	C= 101 Pb= 97	N.S.
					California Personality	C= 80 Pb= 72	N.S.
					Frostig Perceptual Quotient	C= 100 Pb= 103	N.S.
					Finger-Thumb Apposition	C= 27 Pb= 29	N.S.

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[a] Mean test scores obtained for control children are indicated by C = $\bar{x}$; mean scores for respective lead-exposed groups are indicated by Pb = $\bar{x}$ (except for Rummo[211] study where C = control, S = short-term lead-exposed subjects; L = long term lead-exposed group and P = post-encephalopathy lead group).

[b] N.S. = non-significant, i.e. $p > .05$. Note exception of $p < .05$. Note exception of $p < .10$ listed for spatial ability results in Kotok et al.[232] study.

[c] Urinary coproporphyrin levels were not elated.

[d] Or 30 µg/dl or above with positive radiologic findings. The latter suggest earlier exposure in excess of 50-60 µg/dl.

[e] Assays for lead in teeth showed the Pb-exposed group to be approximately twice as high as controls (202 µg/g vs. 112 µg/g, respectively).

[f] Used for children over 5 years of age.

[g] Used for children under 5 years of age.

astrocytosis and glial nodules were found in white matter along with perivascular exudate.

Lead encephalopathy in the mouse was first described by Rosenblum and Johnson[250] who, like Pentschew and Garro, used the suckling animal. In contrast to the rat brain, the striatum and cerebellum of mice fed either 0.5 or 1 percent lead carbonate displayed only faint staining with Trypan Blue (except for a single animal with darkly stained cerebellum) and only occasional paraplegia. The most striking vascular change in the poisoned mice was the appearance of intervascular strands throughout the brain, especially in the hippocampus and basal ganglia. Rosenblum and Johnson[250] concluded that no cerebral edema and focal destructive lesions were found in the mouse brains. Therefore, the histological response of the suckling mouse exposed to lead differs from that seen in the suckling rat. These differences are probably not attributable to different exposure levels (4 percent carbonate in the rat versus 1 percent in the mouse), because the food consumption per unit body weight is three to four times greater in the mouse than in the rat, making the external exposures roughly equivalent.

Wells et al.[251] have recently reported on experimental lead encephalopathy in calves. Four Jersey bull calves were exposed to 20 mg/kg/day of lead acetate, beginning at 3 months of age and lasting for 8 to 273 days. Histological evaluation of the brains of exposed animals revealed focal vacuolation of the neuropil, neuronal necrosis, and changes in the capillary walls in the cerebral cortex and in subcortical areas. Lesions in these cattle were similar to those seen in children with lead encephalopathy in that both show not only vascular changes in the brain with edema but also areas of neuronal necrosis.

In summary, the histopathological changes associated with lead encephalopathy vary among species and are characterized by their relative involvement of neuronal degeneration and vasculopathy. The fact that lead encephalopathy is reported to occur in the absence of cerebral edema in man,[198] mouse,[250] and guinea pig[252] is argument for a direct neuronal involvement of lead. Recent studies have, in fact, suggested direct neuronal alterations by lead. Bull et al.[253] reported that lead interferes with potassium-stimulated respiration of rat cerebral cortex slices, and Nathanson et al.[17] reported that lead inhibited brain adenyl cyclase *in vitro*. No distinction can be made in these studies, however, between neuronal and other cell types. Thus, a direct biochemical effect of lead on the neuron cannot be definitively concluded from these studies.

The relative involvement of the capillary bed in the lead encephalopathy may depend on the degree of maturation at the time of exposure. Bouldin et al.[252] for example, were able to produce lead encephalopathy in adult guinea pigs with no cerebral edema or increased capillary permeability, whereas the suckling rat shows these effects almost exclusively.

Since the initial description of lead encephalopathy in the rat by Pentschew and Garro,[52] considerable effort has been made to define more closely the extent of CNS involvement at subencephalopathic levels of lead exposure. This experimental effort has focused almost exclusively on the developing organism. The interpretation of a large number of experiments dealing with early exposure to lead have, however, been confounded by a number of flaws in experimental design.

Perhaps the most notable of these experimental shortcomings has been the presence of undernutrition in experimental animals. Changes in nutritional status during early brain development are known to produce changes in behavior.[254,255] Castellano and Oliverio,[256] for example, reported a marked delay in neurological development, an increase in exploratory locomotor activity, and a lowered avoidance performance in mice that were undernourished during early development by being reared in large litters. Neurochemical processes have also been shown to be affected by early undernutrition. Eckhert et al.[257] reported changes in cholinergic enzyme activities when rats were placed on protein-deficient diets during various periods of development. Their results indicate that "the relationship between the activity of individual cholinergic enzymes, nutritional status and developmental age is complex and is not the same for different brain regions or even the same brain region exposed to undernutrition during different periods of development." Therefore, in reviewing the animal literature concerned with the neurotoxicology of lead exposure, the possible contribution of undernutrition must be considered. Furthermore, the possibility also exists that lead and undernutrition may be having a synergistic effect on nervous system development. In this case, the methods of pair-feeding currently employed in some studies[247,258] may not provide adequate control for this undernutrition. Examples of dietary factors known to affect susceptibility of lead toxicity have been reviewed by Goyer and Mahaffey.[259]

Animals fed diets containing lower than recommended concentrations of nutrients generally retain higher concentrations of lead in tissues than animals on normal diets.[259] However, almost nothing is known about the effects of elevating nutrient intake above recommended levels — which is the case with most commercial laboratory chows — on the toxicity of lead. Additional research is needed in this area, and until further data are available on the influence of varying degrees of overnutrition, variation in nutrient intake must be suspected of altering the toxicity of lead.

11.5.2.1 DEVELOPMENT

Several laboratories have reported on the effects of perinatal lead exposure on physical, reproductive, and neurological development.[247,250,260,261] Unfortunately, in a number of studies either no control was provided for undernutrition,[250,260,262] or undernourished pair-fed controls showed similar developmental delays,[247] thus masking any direct effects of lead.

Maker et al.[263] also examined the effects of lead exposure on brain development in mice. Two methods were used in an attempt to control for the effects of early undernutrition. In the first experiment, two pair-fed litters were used. Pair-feeding was accomplished by allowing a litter access to an amount of normal chow equivalent to that consumed by a litter on a 0.8 percent lead diet. Both pair-fed litters showed a reduction in brain weight at 30 days of age, as did the lead-treated animals. The two pair-fed litters, however, differed in the relative reduction in brain weight, one showing an identical response to the lead-treated groups and one showing brain weights intermediate between controls and lead-treated animals. A second attempt to alter the nutritional state of the animals was accomplished by altering litter sizes (3 pups versus 6 pups). Body weights of control animals of the two litter size groups were equivalent, however, so that varying the litter size over this range did not effectively produce undernutrition. Therefore, the conclusion of Maker et al.[263] that underconsumption of food alone does not account for the slow development of litters on a lead diet is not supported by their data.

Reiter et al.[264] examined development in rats exposed to lead both prenatally and during lactation via the mothers' milk. They reported a delay in both the age at eye opening and the age at development of the air righting reflex in the 50 ppm treatment group. This exposure level was shown to produce no depression in growth, which suggested a direct effect of lead on nervous system development. No difference in the development of the acoustic startle response was observed. Kimmel et al.,[265] using a similar experimental design, also reported delays in both surface and air righting in rats exposed to 50 or 250 ppm lead; and no differences were found in either auditory startle, pinna detachment, eye opening, ear opening, or incisor eruption.

Sexual maturation appears to be one aspect of development that is quite sensitive to disruption by lead exposure. Kimmel et al.[265] reported a dose-related delay in vaginal opening in female rats exposed to 25, 50, or 250 ppm lead acetate in the drinking water starting at conception. In the group exposed to 25 ppm lead, no differences in growth rates were observed. This suggests a direct effect of lead on sexual maturation rather than a change secondary to body weight changes.

Der et al.[266] reported on the combined effect of parenteral administration of lead acetate and low protein diet (100 μg subcutaneously daily, ages 20 to 61 days) on sexual development in the Sesco rat. Lead significantly delayed the age at which vaginal opening occurred in animals on the control diet. Females given lead in combination with low protein diets did not exhibit vaginal opening through 61 days of age. The authors interpret these data on the basis of a lead/protein-deficiency interaction. However, since animals were given 100 μg of lead per day regardless of body weights and since their body weights were at 26 percent of control, the dosage of lead per unit body weight was 400 percent greater than lead-treated animals on a control diet, which may account for the additional delay in maturation.

Gray and Reiter[261] studied the effects of lead administration (5 mg/ml in the drinking water at parturition) on sexual maturation in the mouse. Vaginal opening was delayed about 4 days in lead-treated animals. No delay in development was seen in pair-fed controls, further suggesting a primary effect of lead on sexual maturation. Furthermore, no delay in sexual maturation was observed in animals when lead was discontinued at weaning. Therefore, the presence of lead at the time of maturation appears essential for the lead-induced delay and may be related to its effects on circulating hormones at the time of puberty.

11.5.2.2 LOCOMOTOR ACTIVITY

In the animal model, the most commonly employed behavioral index of lead toxicity has been locomotor activity. As with other behavior, locomotor activity is influenced by a variety of factors that include sex, age, time and duration of testing, type of measurement, etc. The relative influence of these factors on the observed activity will vary with the experimental method employed. The endpoint being measured is activity (not necessarily ambulation), and the nervous-system processes responsible for this activity and their relative contributions may be different. Tapp,[267] for example, compared seven different measures of activity in the rat and found virtually no intercorrelation. These results suggest that the tests he employed were not measuring the same behavior. Capobianco and Hamilton[268] examined the effects of various brain lesions on ambulation as measured by three different methods: open-field, stabilimeter, and activity wheels. These different measures of activity were affected differently by a given brain lesion. Lesions of the diagonal band, for example, produced increased activity in the running wheel, decreased activity in a stabilimeter, and no change in activity in an open field.

Not only is the type of activity-measuring device important, but also of importance is the length of time over which the activity is measured. Short-term measurements of activity in a novel environment have been termed exploratory activity or locomotor reactivity and primarily reflect the animal's reaction to the novel environment. This reactivity in turn will be affected by the structure of the environment. In order to determine spontaneous or basal activity levels, an animal must reside in an environment over long periods of time. Once the animal is established in the environment, the activity levels of the animal, especially the rodent, will be highly dependent on the time of day.

Therefore, in reviewing the lead literature, it must be remembered that locomotor activity measurements do not represent a unitary behavior; careful consideration must be given to the particular experimental methods employed. In addition, attempts to extrapolate the results of an activity measurement in animals directly to the clinical situation are unwarranted. A brief summary of pertinent studies is given in Table 11-5.

TABLE 11-5. EFFECTS OF LEAD EXPOSURE ON LOCOMOTOR ACTIVITY IN LABORATORY ANIMALS

Reference	Species	Exposure conditions	Lead concentration, μg %		Test conditions, in order of presentation 1. Method 2. Length of testing 3. Group size 4. Age	Nutritional status	Results
			Blood	Brain			
Allen et al.[269]	Monkey	0.5-9 mg/kg/day for 12 weeks	160-400		Observed locomotor activity	Normal	Hyperactivity (qualitative measures)
Bornschein et al.[270]	Mouse, (Charles River) CD-1	5 mg/ml lead acetate in drinking water, starting at parturition	120-190	200-306	Proximity counter 3 hours Individual 35 days	Undernourished	Normal
Brown[271]	Rat (Bar F - Rabbitry)	35 mg/kg P.O. to dams from parturition to 21 days			Photoactometer 20 min Individual 49 days		Normal
Driscoll and Stegner[272]	Rat (Simonsen)	10^{-4} and 10^{-2} M lead acetate in drinking water from conception			Open-field 2 min Individual 31 days	Undernourished	Hypoactive (61% of control)
Gray and Reiter[261]	Mouse, (Charles River) CD-1	5 mg/ml lead acetate in drinking water, starting at parturition			Residential maze 90-240 min Individual 30, 50, 130 days	Undernourished	Hypoactive (75-80% of control)
Hastings et al.[273]	Rat, (Long-Evans, Charles River)	0.2 or 1.0 mg/ml from parturition to 21 days	Control = 11± 4 0.2 mg/ml = 29± 5 1.0 mg/ml = 42± 4		Running wheel 3 weeks Individual 30-51 days	Normal	Normal
Kostas et al.[274]	Rat (Long-Evans) Blue Spruce	0.05-5.0% lead acetate in mother's chow from parturition until 21 days. Continued in offspring at 0.25-25 ppm in chow until 35 days			Shuttle box, activity wheel 1 hr Individual 75-77 days; 90-93 days	Normal - 0.05% group undernourished in 5-5.0%	Hyperactivity in shuttle box (182% of control). Normal in activity wheel.

(continued)

TABLE 11-5 (continued).

Reference	Species	Exposure conditions	Lead concentration, µg %		Test conditions, in order of presentation: 1. Method 2. Length of testing 3. Group size 4. Age	Nutritional status	Results
			Blood	Brain			
Overman[275]	Rat, (Long-Evans Charles River)	10, 30, 90/mg/kg/day by intubation from 3-21 days of age	21 days 90 mg/kg = 226± 21 35 days 90 mg/kg = 56± 5		Jiggle platform Four days Individual 22-65	Normal	Hyperactive
Reiter[258] Reiter et al.[276]	Rat, Sprague Dawley, Charles River	5% lead carbonate in mother's chow from parturition to 16 days, 50 ppm in drinking water for remainder of experiment			Jiggle cage; Residential maze 4 min; 14 days Individual; group of 3 13-44 days; 120-160 days	Undernourished	Transient hyperactivity (200% of control at 13 days). Normal at 44 days. Normal levels in adults; but disrupted ultradian rhythms.
Reiter et al.[264] Cahill et al.[277]	Rat, Sprague Dawley, Blue Spruce	5,50 ppm in drinking water. 40 day pretreatment of parents. Continued from conception through adulthood	180 day males 0= 5± 0.5 5= 6± 0.4 50= 10± 0.6	180 day males 0= 18± 1 50= 20± 2 50= 27± 2	Residential maze 5 days Groups of 3 120 days	Normal	Hypoactivity (53-78% of controls)
Reiter et al.[264]	Mouse, Charles River, CD-1	5 mg/ml lead acetate in drinking water from parturition until 45 days			Residential maze 2 days Individual 100 days	Undernourished	Normal
Sauerhoff and Michaelson[278] Sauerhoff[279]	Rat, Sprague Dawley, CO	4% lead carbonate in mothers' chow from parturition to 16 days post-partum, 40 ppm in drinking water		29 days 88± 1.1	Selective activity meter 24 hours Groups of 6 26-29, 50	Undernourished	Hyperactive at 29 days (140-190% of control) Normal at 50 days
Silbergeld and Goldberg[262,280,281]	Mouse, Charles River, CD-1	2, 5, 10 mg/ml lead acetate in drinking water starting at parturition			Proximity counter 3 hours Individual 30-150 days	Undernourished	Hyperactivity (300-400% of control)
Sobotka and Cook[282] and Sobotka et al.[283]	Rat, Sprague Dawley (Charles River)	8-91 mg/kg/day by intubation from 3-21 days of age	22 days 81 mg/kg = 71± 12 35 days 81 mg/kg = 23± 1.4		Photoactometer 30 min Individual 24-28 days	Normal	Normal
Sobotka et al.[284]	Dog (Beagle)	1 or 4 mg/kg/day orally from 2 weeks to 5 months			Open field — Individual 3-4 months	Not indicated	Hypoactive
Winneke et al.[285]	Rat (Wistar)	1.38 g lead acetate/kg of chow (745 ppm Pb) for 60 days pretreatment to mothers. Continued in offspring from conception to testing	16 days 26.6 190 days 28.5		Open field 3 min, on consecutive days Individual 90-140 days	Normal	Hyperactive (129% of control)
Zenick et al.[286]	Rat, Sprague	750 or 1000 mg/kg/day to females on restricted watering schedule from 21-99 days of age. Exposure continued through gestation and weaning.			Open field 3 min, on 10 consecutive days Individual 22-32 days	Undernourished	Initial hypoactivity in 100 mg/kg group (days 1 and 2) Hyperactive by the 7th test day.

The data to be reviewed here suggest that perinatal lead exposure produces an altered reactivity of an animal to a novel environment. Reactivity is increased in the young animal, but this increased reactivity disappears as the animal matures. In the adult animal, on the other hand, the lead exposure results in a reduced reactivity. As will be seen, the exact nature of the change in locomotor activity brought about by this altered responsiveness will depend heavily on the structure of the test environment.

Sauerhoff and Michaelson[278] and Sauerhoff[279] exposed lactating females to lead using a modification of the Pentschew and Garro[52] exposure regimen. Litter mates were tested as a group at 25 to 28 days of age in a test case similar to the home cage. The data were collected in four blocks of 3 hr and one block of 12 hr, extended over 4 days. Although they are presented as counts per hour for a 24-hr period, data represent reactivity attributable to multiple short-term exposures to a novel environment, and, therefore, are not comparable with data obtained by continuous sampling over a 24-hr period. Offspring of a lead-exposed mother exhibited elevated activity levels. Since only one group (n = 6 pups) was tested from each treatment, however, no statistical test can be applied to these data.

Using a similar exposure regimen, Reiter[258] and Reiter et al.[276] exposed animals to 5 percent lead carbonate in the chow starting at parturition. Animals were repeatedly tested at various ages, beginning at 13 days of age, using a 4-min jiggle platform activity measurement. This measuring device detects both locomotor activity and stationary body movements. They reported an increased activity (200 percent of control) in 13-day-old animals. This elevated activity declined with age and returned to control levels by 44 days of age. Comparisons were made with pair-fed controls since this exposure resulted in a significant growth impairment. Whether this return to normal levels was caused by maturation or by repeated testing was not determined in this study. Animals were also tested as adults (120 days) in a residential maze, which allows continuous measurement of activity over extended periods of time; this test showed no differences in the activity levels as a result of treatment. However, the ultradian rhythms of activity seen in control animals during the nocturnal period (short-term, 4/hr oscillation in activity) were absent in lead-exposed animals.

Overmann[275] used a similar jiggle platform to measure activity in 22- to 65-day-old rats. As in the Sauerhoff and Michaelson study,[278] animals were rotated between testing cages, and, therefore, the observed increase in activity was consistent with a lead-induced change in locomotor reactivity. In this experiment, pups were directly exposed by daily intubation ranging from 10 to 90 mg/kg/day. This exposure is similar to that used by Sobotka and Cook,[282] who employed intubation levels of 9 to 81 mg/kg/day, but who reported no differences in activity in a photoactometer.

One striking difference between these two experiments was in the reported blood lead levels, shown in Table 11-6. Therefore, the higher internal exposure seen in Overmann's experiment may have accounted for the difference in the observed behavioral effects, although differences in experimental protocol may also have accounted for differences in the behavioral effects.

TABLE 11-6. LEAD EXPOSURE AND RESULTING BLOOD LEAD LEVELS IN EXPERIMENTS MEASURING LOCOMOTOR ACTIVITY IN RATS

Experiment	Blood lead, μg/dl	
	21 to 22 days	35 days
Sobotka and Cook [282] and Sobotka et al.[283] (81 mg/kg/day)	71 ± 12.4	23 ± 1.4
Overmann[275] (90 mg/kg/day)	226.1 ± 21.1	56 ± 4.6

Two different laboratories have reported on the effects of lead administration on open-field activity in 30- to 40-day-old rats. Driscoll and Stegner[272] reported a decreased activity in animals tested for 2 min. Zenick et al.[286] tested animals for 3 min in an open field on 10 consecutive days. On the first 2 days of testing, animals from the high exposure group (1000 mg/kg/day in the drinking water of the mother) showed a decreased activity similar to that reported by Driscoll and Stegner.[272] By the seventh day of testing, however, these animals were ambulating at a higher level than controls. These data can also be interpreted as an increased locomotor reactivity in lead-treated animals that is initially manifested in an open field as decreased ambulation. With repeated exposure, the animals show an elevated activity similar to that in previously reported studies. The difference in the direction of lead-induced change in initial activity levels in these open field experiments as compared to the jiggle platform experiments[258,275] is probably a result of the differences in the size of the test environments. The larger open field results in decreased activity in lead-exposed hyperreactive animals, whereas in the smaller jiggle platform the animals show increased activity.

Finally, Hastings et al.[273] reported no differences in running-wheel activity of 30-day-old animals exposed to lead by suckling with mothers receiving 1 mg/ml lead in the drinking water. This exposure resulted in blood lead values of 42 μg/dl at weaning. Since animals do not normally show much running activity upon initial exposure to the running wheel, the effects of this lead exposure on reactivity cannot be adequately tested. These results do demonstrate that long-term running wheel activity (3 weeks) was not disrupted in these young, lead-exposed animals.

At or about the time of sexual maturation, lead exposure has not been shown to alter activity levels in the rat. As previously indicated, Sauerhoff and Michaelson[278] and Reiter et al.[276] found no differences in activity in animals tested between 44 and 50 days of age. These were animals which were reported to have increased activity at a younger age. Brown[271] also reported no differences in locomotor activity in animals tested at 49 days of age either in an photoactometer or in an open field.

Available data also suggest that perinatal exposure to lead may produce a decreased reactivity in the adult animals. Kostas et al.[274] measured locomotor activity in adult rats exposed to either 0.05, 0.5, or 5.0 percent lead carbonate in the chow from parturition until weaning and to 0.25, 2.5, or 25 ppm from weaning until 35 days of age. Two measurements of activity were employed. Animals tested for 1 hr in a shuttle box activity cage were found to have increased activity, whereas animals tested in running wheels showed no difference from controls. This lack of sensitivity of the running wheel to lead-induced changes in activity is consistent with the finding of Hastings et al.[273] Again, the nature of the change in shuttle box activity may be interpreted in terms of a lead-induced decrease in reactivity toward a novel environment, since rats made more reactive would tend to freeze in this environment, thus causing decreased ambulation. Winneke et al.[285] found a similar change in reactivity as indicated by open-field activity scores over 5 successive days of testing. Lead-treated rats had significantly elevated activity on the first 3 days of testing, and activity had returned to normal on days 4 and 5.

Reiter et al.[264] reported a lead-induced decrease in activity in adult animals tested in a residential maze. This test system allowed for measurement of various components of the animals' activity, including exploratory, diurnal, and nocturnal activity. Exploratory activity was initially suppressed in lead-treated animals, but this difference disappeared as the animals became established in the environment. On the other hand, activity levels remained suppressed during the nocturnal period.

In a second study, Reiter et al.[276] reported no difference in residential-maze activity of adult lead-treated animals. They speculated that the lack of a lead effect on locomotor activity in the second experiment may have been the result of the choice of animal supplier (Charles River). Since the Charles River animals were normally less active in the maze, it may have been difficult to lower their activity further with treatment. Differences in experimental protocol, i.e., differences in dose and period of exposure, however, also may have accounted for the differences in observed activity.

In summary, data on the rat suggest that perinatal exposure to lead may produce an increased reactivity which disappears as the animal matures. This effect could result from a delay in normal maturation of forebrain inhibitory systems.[287] As the lead-treated animals mature, they pass through a period of normal reactivity which then progresses to a decreased reactivity in the adult animal. These data would be consistent with a maturational lag seen in children[288] and pose an interesting hypothesis that requires further testing.

Sobotka et al.[284] have reported decreased ambulation in young dogs exposed to lead and tested in a 7- by 7-ft open field. Allen et al.[269] exposed infant monkeys to lead via their formula and reported hyperactivity from 3 to 5 months of age. These data and the data of Sobotka et al.[284] are consistent with the lead-induced increase in reactivity seen in the young rat. The data of Allen et al.[269] must be qualified, however, since no quantitative measure of activity was made.

In a series of often cited papers, Silbergeld and Goldberg[262,280,281] reported lead-induced hyperactivity in mice. Lactating females were exposed to lead acetate in the drinking water, starting at parturition, in concentrations of either 2, 5, or 10 mg/ml. The authors reported a 300- to 400-percent increase in locomotor activity that extended from 30 to 150 days of age in the offspring. The lack of a control for the growth retardation found in the lead-treated groups makes interpretation of these data difficult. As previously indicated, Castellano and Oliverio[256] reported that early undernutrition produces hyperactivity in mice. Therefore, the observed hyperactivity may have resulted from the undernutrition, independent of a lead effect. Greater concern, however, stems from the subsequent failure of two different laboratories[261,270,289] to replicate the findings of Silbergeld and Goldberg, using the same strain of mouse and the same exposure regimen.

Bornschein et al.[270] exposed lactating mice to 5 mg/ml lead acetate and tested offspring in activity chambers identical to those employed by Silbergeld and Goldberg.[262,280,281] They were unable to verify lead-induced hyperactivity in mice even though undernutrition was also present in their animals.

Gray and Reiter[261] were also unable to demonstrate hyperactivity in lead-exposed mice, using a residential maze to measure activity. Furthermore, Reiter et al.[289] were unable to find differences in the activity of mice experimentally exposed to lead from birth to 45 days in Goldberg's laboratory and then transported to the author's laboratory for behavioral testing.

Silbergeld and Goldberg[280,281] also studied the locomotor response of lead-exposed mice to various drugs that are used in the treatment and diagnosis of minimal brain dysfunction in children. Most notably, they reported that their lead-treated, hyperactive mice responded paradoxically to the stimulants amphetamine and methylphenidate. Examination of the activity data following administration of methylphenidate[281] raises questions as to the exact nature of the paradoxical response. Both control and lead-treated animals responded with increased locomotor activity following 40 mg/kg of methylphenidate; however, the response of the lead-treated mice was markedly attenuated. Within 90 to 120 min, animals were below their predrug level. This time course in the response would be expected if the lead-treated animals were entering into stereotypic behavior (a behavioral pattern characteristically seen following high doses of amphetamine-like compounds).[290] Although the authors state that no stereotypic behavior occurred in lead-treated animals, no quantitation of this behavior was made. Furthermore, this stereotypic behavior has been observed in lead-treated mice by other investigators.[270] Again, the possible contribution of early undernutrition to these results must be considered. Bornschein et al.[270] found this paradoxical lowering of activity in undernourished mice following 10 mg/kg of d-amphetamine, but only during the second hour following drug administration. In the first hour, activity showed the expected increase, although to a lesser extent than in controls. These authors postulated that early undernutrition shifts the dose-response curve to the left such that animals given high levels of amphetamine (10 mg/kg) enter into stereotyped behavior sooner than controls, which prevents the occurrence and the recording of locomotor activity.

Reiter[258] examined the dose-response relationship to amphetamine in control, undernourished, and lead-exposed rats. He found, as did Bornschein et al.,[270] that undernutrition shifted the dose-response curve to the left. Lead treatment, on the other hand, shifted the dose-response curve to the right. Thus, under the appropriate conditions, lead exposure per se can be shown to produce an attenuated response to amphetamine. The occurrence of a true paradoxical response, however, is questionable.

The lead-induced attenuated response to amphetamine has been observed regardless of whether the reported predrug activity levels were elevated,[280,281] normal,[258,282] or depressed.[264] The determination of the exact nature of this altered response, i.e., altered CNS sensitivity versus altered absorption, distribution, and metabolism, requires further study.

11.5.2.3 LEARNING ABILITY

There is little doubt that acute, high-level lead exposure in young children can produce overt manifestations of neurotoxicity.[182,203] Mental retardation is an established sequela of lead-induced encephalopathy in children.[85,86] The extent and nature of lead-induced neurotoxicity following long-term low-level lead exposure during the developmental years is also of continuing interest. As indicated previously, restrospective studies in children are generally equivocal and are compromised by serious experimental design limitations, e.g., unsatisfactory documentation of lead-exposure history prior to behavioral testing and inappropriate or unsatisfactory control groups.[291]

In an attempt to overcome some of these limitations, investigators have turned to animal models of chronic, low-level exposure. The major portion of this work has been carried out in rats. Table 11-7 provides a summary of the pertinent studies, including exposure conditions, testing conditions, and results. In an attempt to structure this literature and facilitate evaluation, the organization shown in Table 11-8 has also been developed. It separates the data along two lines: (1) tasks that reportedly are, or are not, sensitive to changes arising from the exposure conditions and (2) the stage of learning during which effects are, or are not, demonstrable. The acquisition column indicates investigations of the rate at which animals form associations between stimulus and reinforcement conditions. Measures utilized to quantify the process are numbers of days and trials or problem presentations required to reach some predetermined level of performance. The percentage of the test population attaining the defined criterion per unit time is also a common measure. The performance column includes studies of the quantitative nature of the behavior after the desired criterion has been attained. The reversal/extinction column contains studies of behavior observed following the removal of (extinction) or alteration of (reversal) the conditions that produce reinforcement.

TABLE 11-7. PROTOCOLS USED FOR THE STUDY OF ANIMAL LEARNING

		Behavioral task			Lead exposure		Number			Blood lead, μg/dl		
Reference	Species	Apparatus	Reward	Task^a	Period^b	Level^c	Litter per test group	Subjects per test group	Growth^d rate	Peak	At test	Learning performance
Brady et al.[292]	Rat	water T-maze	neg.	Simult. B.D.	PG,G,L	500 GAV^e	4	17	N	?	?	Impaired
Brown, D.[271]	Rat	T-maze	pos.	Succ. B.D.	L	100 W^f	?	6	N	?	?	Impaired
		T-maze	pos.	Succ. B.D.	L	25 GAV^e	?	?	N	?	?	Impaired
		T-maze	pos.	Succ. B.D.	L(1st 10d)	35 GAV^e	?	5-6	N	46	?	Impaired
		T-maze	pos.	Succ. B.D.	L(last 11d)	35 GAV^3	?	5-6	N	20	?	No effect
		T-maze	pos.	Succ. B.D.	L(last 11d)	70 GAV^e	?	5-6	N	19	?	No effect
		T-maze	pos.	Succ. B.D.	L(last 11d)	140 GAV^e	?	5-6	A	?	?	Impaired
		T-maze	pos.	Succ. B.D.	Birth to day 10	5 IP^e	?	7	N	288	23	Impaired
Brown, S. et al.[293]	Rat	water T-maze	neg.	Spatial discrim.	Various (8 days to 5 weeks)	100 IP^e	?	66	?	?	?	No effect
		Shuttle-box	neg.	2-way	5 weeks	100 IP^e	?	8	?	?	?	No effect
Driscoll and Stegner[272]	Rat	Y-maze	pos.	Simult. B.D.	PG,G,L,PW	2070 DT^i	?	4	A	?	?	Impaired
		Shuttle-box	neg.	2-way	PG,G,L,PW	2070 DT^i	?	5	A	?	?	Improved
		Shuttle-box	neg.	2-way	PG,G,L,PW	2070 DT^i	?	12	N	?	?	Impaired
		Shuttle-box	neg.	2-way	PG,G,L,PW	2070 DT^i	?	12	A	?	?	Improved
Overmann[294]	Rat	E-maze	pos.	Spatial discrim.	L	5,16,49 GAV^i	?	?	N	33,174 226	15,23, 56	No effect
		E-maze	pos.	Tactile discrim.	L	5,16,49 GAV^i	?	?	N	33,174 226	?	Impaired on reversal
		E-maze	pos.	Visual discrim.	L	5,16,49 GAV^i	?	?	N	33,174 226	?	No effect No effect
		2-compartment chamber	neg.	1-way	L	5,16,49 GAV^i	?	?	N	33,174 226	?	Impaired
		2-compartment chamber	neg.	Passive avoid	L	5,16,49 GAV^i	?	?	N	33,174 226	?	No effect
		Operant	pos.	Temporal disc.	L	5,16,49 GAV^i	?	?	N	33,174 226	?	Impaired
Snowdon[295]	Rat	CF maze	pos.	Maze learning	Adult exposure and PW	2.7,4.4 6.6 IP^e	?	8-10	A	?	?	No effect
		CF maze	pos.	Maze learning	L	4.4 IP^e	17	36	A	?	?	Impaired
Sobotka et al.[283]	Rat	Shuttle-box	neg.	2-way	3-21 days post-partum	5.15,44 GAV	6-7	28-34	?	11 21 23	?	Impaired

(continued)

TABLE 11-7 (continued).

		Behavioral task			Lead exposure		Number			Blood lead, µg/dl		
Reference	Species	Apparatus	Reward	Task[a]	Period[b]	Level[c]	Litter per test group	Subjects per test group	Growth rate	Peak	At test	Learning performance
Sobotka and Cook[282]	Rat	2-compartment chamber	neg.	passive avoid	3-21 days post-partum	5,15,44[e] GAV	?	5-8	N	18,61,71	?	No effect
		Shuttle-box	neg.	1-way	—	—	?	5-8	N	18,61,71	?	No effect
		Shuttle-box	neg.	2-way	—	—	?	5-8	N	18,61,71	?	Impaired
		Operant	neg.	Spatial discrim.			?	5-8	N	18,61,71	?	Impaired reversal
Slecta[296]	Rat	Operant	pos.	FI schedule	PW (day 22-57)	50,300 1000 W[f]	—	3	?	9,28,40	?	Altered
Shapiro et al.[297]	Rat	Operant	pos.	VI 30 schedule	PW (day 90-126)	.09 - 52 IP[e]	—	7	?	?	?	Altered
Hastings et al.[273]	Rat	Shock grid	neg.	Flinch	L	109, 546 W[f]	3	10	N	29,42	5,9	No effect
		Shock grid	neg.	SEA	L	109, 546 W[f]	3	10	N	29,42	5,9	Less aggressive
		Operant	pos.	Succ. B.D.	L	109, 546 W[f]	3	10	N	29,42	5,9	No effect
Winneke et al.[285]	Rat	Lashley jumping stand	pos.	Simult. PD & SD	PG,G,L PW	745 DT[f]	—	10	N	29	29	Impaired
Bornschein[298]	Mouse	Operant	pos.	Simult. B.D.	L	103,546 2730 W[f]	5	15	A	79 -190	29,120	Impaired
Bornschein[299]	Mouse	Operant	pos.	Simult. B.D.	L	109,546 W[f]	7	14	N	80 180	29	Impaired reversal
Sobotka et al.[284]	Dog	T-maze	pos.	Simult. R.D.	2-week-5 month post-partum	1.4 W[f]	—	10	N	85	—	Impaired
VanGelder et al.[300]	Sheep	Operant	pos.	Auditory discrim.	Adult exposure 9 weeks	100 GAV[e]	—	4	?	?	?	Impaired
		Operant	pos.	FI schedule		1000 DT[f]	—	5	?	30	30	No effect
		Operant	pos.	FI schedule		530 DT[f]	—	5	?	17	17	No effect
Carson et al.[301,302] and VanGelder et al.[300]	Sheep	CF maze	pos.	Maze learning	G	2.3,4.5[e] DT	—	6-8	?	17-25	9-14	No effect
		CF maze	pos.	Maze learning	5 days-12 weeks post partum	2,4,8,16[e] DT	—	4	?	57,81 123,162	—	No effect
		Operant	pos.	Simult. FD & SD	G	2,3,4,5[e] DT	—	6-8	?	17,25	9,14	Impaired
Bowman and Bushnell[303]	Monkey	WGTA	pos.	—	L,PL	0.3,1.0	—	4	—	50,85	50,85	Impaired reversal

[a] Succ. B.D. = Successive brightness discrimination.
Simult. B.D. = Simultaneous brightness discrimination.
1-way = One-way avoidance.
2-way = Two-way avoidance.
FD = Form discrimination.
SD = Size discrimination.
Flinch = Tail-flinch test.
SEA = Shock elicited aggression.
CF maze = Close-field maze.
Operant = Operant chamber.
WGTA = Wisconsin General Test Apparatus.

[b] PG= Pregestation period, external exposure to dam.
G= Gestation period, external exposure to dam.
L= Lactation period, external exposure to dam.
PW= Post weaning period, external exposure to pup.

[c] DT= Diet
GAV= Gavage
IP= Intraperitoneal
W= Drinking water

[d] N= Normal
A= Altered

[e] mg/kg/day

[f] ppm

A review of the studies listed in Table 11-7 leads to the following general critique. Few animal studies adequately simulate the lead exposure conditions found in young children either with respect to the levels of exposure or the timing of the exposure. There is often an inadequate or nonexistent history of lead exposure with respect to both the external and internal dose. In regard to the general experimental designs, several design deficiencies frequently occur. These include: (1) limited sample size or larger samples derived from a few litters — the latter permits genetic effects to have an inordinate influence on the results — and (2) inappropriate application of statistical methods and confounding of variables, e.g., maternal undernutrition or neonatal growth retardation, which results in an inability to determine specific causes for demonstrated effects. The selection of behavioral tasks is often made with little or no apparent rationale that would aid in the formulation and testing of hypotheses and interpretation of data. Finally, most investigators do not provide adequate documentation of the relative sensitivity of the behavioral tasks being used which could be accomplished with the use of a standard reference compound. Since this has not been done, failure to observe a disruption in task acquisition or performance could be taken to mean that (1) the task is not sensitive enough to detect the deficit or (2) the neural systems which mediate the behavior on that task are not affected by lead at the exposure levels examined.

In spite of the extensive methodological differences in these studies, several conclusions can be drawn from the data shown in Tables 11-7 and 11-8.

TABLE 11-8. STAGE OF LEARNING

Treatment effects	Acquisition	Performance	Reversal extinction
Present	Brady et al.[292.a] Brown[304.b] Carson et al.[301.b] Driscoll and Stegner[272.a.b] Hastings et al.[273.b] Overmann[294.a] Snowdon[295.b] Sobotka et al.[283.a] Winneke et al.[285.b] Miller et al.[305.b]	Shapiro et al.[297.b] Slecta[296.b] Bornschein et al.[298.b]	Overmann[294.a.b] Sobotka et al.[283.a] Bornschein et al.[298.b] Bowman[303.b]
Absent	Bornschein et al.[298.b] Carson et al.[300.b] Hastings et al.[273.b] Overmann[291.a.b] Sobotka et al.[283.a] Winneke et al.[285.b]		Overmann[294.a] Sobotka et al.[283.a] Miller et al.[305.b]

[a] Negative reinforcer.
[b] Positive reinforcer.

Although learning paradigms are being used to demonstrate effects of lead on CNS function, the present data do not permit a clear distinction between the effects of lead exposure on cognitive function (learning/memory) and effects on sensory-motor function, arousal, or motivation, which in turn can produce performance differences. Therefore, some of the studies appearing in the column titled "Acquisition" (Table 11-8) may, in fact, belong in the "Performance" column. This is especially true of studies that report large group differences on the first day of acquisition (cf. 292, 299). New studies specifically designed to test for this distinction must be conducted.

Tasks that use both positive and negative reinforcers appear to be equally sensitive to disruption following lead exposure (Table 11-8). Therefore, lead exposure does not appear to have a selective effect on a specific motivational system.

Treatment effects have been reported both by those investigators using manual testing procedures which require a high degree of experimenter-subject interaction (cf. 285, 292, 304) and by those using automated operant chambers with minimal experimenter-subject interaction (cf. 283, 294, 306). Thus, reports of significant treatment effects cannot be ascribed to experimenter bias.

The effects appear to persist beyond the immediate exposure period with behavioral disruption demonstrable in animals with normal blood lead levels (cf. 283, 285, 304, 306).

Procedures have been inadequate for reproducing qualitative and quantitative changes in behavior. This has limited the ability to test hypotheses pertaining to the site of action of lead-induced behavioral changes.

It is not yet clear whether the observed effects are direct effects of lead on the developing nervous system or whether the effects are indirectly mediated through treatment-induced alterations in maternal behavior, maternal milk, or one of several potential peripheral target systems in the neonate.

Some types of learning problems appear to be more sensitive to lead-related disruption than others. For example, in the passive avoidance paradigm, acquisition and extinction are reportedly not sensitive.[282,294] Simple pattern discrimination is also apparently insensitive to lead exposure.[285,294,301] Other forms of visual discrimination such as size[285,301] and brightness[272,292,304,306] appear to be particularly sensitive. The two reports of altered size discrimination[285,301] may in fact be special cases of brightness discrimination since the different size stimuli (white pattern on a black background) also reflect different amounts of light. Further testing will be necessary to resolve this issue. Active-avoidance tasks are also being used successfully to examine effects obtained following lead exposure. Both one-way avoidance[294,306] and two-way, shuttle-avoidance tasks[272,283] reflect a disruption in normal behavior. The one exception is a negative finding by Sobotka et al.[283] using a one-way avoidance task. This negative effect may be related to the fact that shock was terminated automatically after 5 seconds, independent of the animals' behavior. This is not the usual procedure, and its effect cannot be evaluated since no data were presented for this particular task.

Deficits in task performance do not appear to be species specific since they are reported for rats,[272,283,294,304] mice,[298] dogs,[305] sheep,[301] and monkeys.[303] Furthermore, recent studies suggest that behavioral alterations may be present in rats exposed to lead following weaning.[296,297] These reports are contrary to the generally held opinion that adult or post-weaning rats are insensitive to lead exposure.[293,295,301] Since the number of reported studies using adult exposure protocols is extremely limited, however, it is not possible to rule out the suggestion that these conflicting data merely reflect differences in task sensitivity. More research using adult exposure protocols and more sophisticated behavioral testing paradigms will be necessary to resolve the conflict.

11.5.2.4 EFFECTS OF LEAD ON AGGRESSIVE BEHAVIOR

Two reports appeared in the literature in 1973 which suggested that lead exposure produced an increased aggressiveness. Silbergeld and Goldberg[262] reported that mice exposed to either 5 or 10 mg/ml of lead had a "heightened frequency of fighting as determined by the incidence of bite frequencies observed on litter-mate males housed together." Sauerhoff and Michaelson[278] also referred to an increased aggressiveness in lead-exposed rats during the fourth week of development. In neither report, however, was there an attempt to quantitate these observations of increased aggression.

Hastings et al.[306] exposed lactating rats to lead (0, 109, or 545 ppm) from parturition to 21 days. This lead treatment produced no change in growth in the offspring. Individual pairs of male offspring (from the same treatment groups) were tested at 60 days of age for shock-elicited aggression. Lead-exposed groups showed significantly less aggressive behavior than the control group. There were no significant differences among the groups in the flinch/jump thresholds to shock. This latter finding suggests that the differences seen in the shock-elicited aggression were not caused by differences in shock threshold.

Gray and Reiter[261] reported on the aggressive behavior of mice exposed to 5 mg/ml lead acetate from parturition. Aggressive behavior was measured by introducing an adult male intruder into the home cage of an individual experimental male. Control males wounded the intruder 85 times on the average during a 14-hour test period, whereas intruders to lead-treated and pair-fed male cages had means of 32 and 35, respectively. Therefore, the reduced aggressive behavior seen in these experiments cannot be explained by lead exposure alone, because similar reductions were observed in pair-fed controls. Nevertheless, in both the rat and the mouse a quantitative examination of aggressive behavior suggests that lead can cause a decrease rather than an increase in aggressive behavior.

11.5.2.5 NEUROCHEMISTRY

The effects of *in vivo* lead exposure on a variety of neurochemical substances and processes have been studied in the past several years (see Table 11-7). Perhaps most notable are the investigations of lead effects on both putative neurotransmitter systems and on energy metabolism in the central nervous system. Much of the work, by its nature, has required the use of experimental animal models for broad screening for possible effects across many different transmitter systems or for testing specific hypotheses of altered transmitter functions. Unfortunately, these studies on the neurochemical effects of lead exposure are hindered by the same problems in experimental design as those discussed in the section on behavioral studies.

Research on neurotransmitter systems has concentrated primarily on the effects of lead exposure on cholinergic and monoaminergic functions, probably because of the extensive background literature that exists on the basic neurochemistry of those transmitters and because of the documentation extant on the neurophysiological and behavioral roles played by these transmitters. The approaches employed in these studies have included: (1) biochemical assays of steady-state levels of transmitter substances in brain tissue;[277,283,288,307-315] (2) assessment of synthesis and turnover rates;[309,315] (3) measurement of the activity of enzymes responsible for transmitter synthesis or degradation;[283,309,311,313,316-318] (4) assessment of transport processes involved in synaptic uptake of transmitters or their precursors;[308,309,316] and (5) assessment of synaptic release mechanisms[308,309,315,316] (see Table 11-9).

TABLE 11-9. *IN VIVO* EFFECTS OF LEAD EXPOSURE ON NEUROCHEMISTRY

Reference	Species	Exposure	Nutritional status	Lead concentration		Neurochemical parameter	Results
				Blood, μg/dl	Brain, μg/g		
Silbergeld and Goldberg[308]	Mouse	5 mg/ml lead acetate in drinking water starting at parturition	Under-nourished	?	?	1) High affinity transport of phenylalanine, glycine, leucine, NE, 5HT, GABA, DA, choline, and tyrosine 2) Steady-state ACh NE DA	1) Decreased high affinity transport of dopamine and choline Increased high affinity transport of tyrosine 2) Increased steady state levels of NE
Silbergeld et al.[309]	Mouse	5 mg/ml lead acetate in drinking water starting at parturition	Under-nourished	?	?	1) ACh release 2) Steady state NE, HVA, VMA 3) MAO 4) Choline transport	1) Decreased 40% 2) Increased 27, 41, 15% respectively 3) Increased 20% 4) Decreased 50%
Carroll et al.[316]	Mouse	2, 5, 10 mg/ml lead acetate in drinking water starting at parturition	Under-nourished	?	?	1) K+ -induced release of ACh and choline 2) Spontaneous release of ACh 3) Steady-state levels of ACh, choline 4) CAT CBK AChE	1) Inhibited K+ -induced release of choline and ACh 2) Increased spontaneous ACh release 3) No change in steady state levels 4) No change
Brown et al.[318]	Rat	7.5 mg/kg (IP) from birth to 10 days of age	Normal	?	?	AChE (regional brain analysis)	No change in medulla oblongata, corpus striatum, cerebellum, cerebrum or hippocampus. Inhibited in midbrain (16%)
Golter and Michaelson[307]	Rat	5% lead acetate in mother's diet from parturition to 16 days post partum, 40 ppm in drinking water Intubated with 1.0 mg/day from parturition to 16 days post partum, 40 ppm in drinking water	Under-nourished	?	?	Steady-state NE, DA	Increased NE at 33 days of age (13%); no change in DA
Michaelson and Sauerhoff[314]	Rat	5% lead acetate in mother's diet from parturition until day 16, 25 ppm in drinking water	Under-nourished	?	Control = 0.1 4% = 0.88	1) Steady-state DA 2) Steady-state 5HT, GABA, and NE	1) Decreased DA (20%) 2) No change
Sauerhoff and Michaelson[278]	Rat	4% lead carbonate in mother's diet from parturition until 16 days, 40 ppm in diet	Under-nourished			Steady-state NE, DA	Decreased DA (20%)
Grant et al.[310]	Rat	0, 25, 100 or 200 mg/kg/day by gavage on postnatal days 3-25	?	0 = 16 25 = 26 100 = 43 200 = 63	0.15 0.38 0.51 0.68	Steady-state NE, DA (regional brain analysis)	No change

(continued)

TABLE 11-9 (continued).

Reference	Species	Exposure	Nutritional status	Lead concentration		Neurochemical parameter	Results
				Blood, μg/dl	Brain, μg/g		
Hrdina[313]	Rat	0.2 and 1.0 mg/kg IP (100g) for 45 days	?	?	?	Cerebro-corticol ACh, AChE	ACh = 32-48% increase AChE - No significant change
				Brain stem NE, 5HT		NE - 20-27% decrease 5HT - No change	
Modak et al.[311]	Rat	1% lead acetate in drinking water at parturition	Under-nourished	Control = 0 1% = 245	?	1) Steady-state ACh 2) CAT 3) AChE	1) Increased ACh in diencephalon (12%) 2) Increased in medulla-pons, hippicampus and cerebral cortex (11-12%) 3) Lower in medulla-pons, midbrain and diencephalon (10-20%)
Sobotka et al.[283]	Rat	8-91 mg/kg/day by intubation from 3-21 days of age	Normal	8-71	—	1) Steady-state NE, DA, 5HT 2) AChE	1) No change 2) Decreased (marginal)
Shih and Hanin[315]	Rat	4% lead carbonate in mother's chow from parturition to 21 days, 40 ppm in diet	Under-nourished	?	?	1) Steady-state ACh, choline 2) ACh turnover	1) No change in ACh, increased choline 2) Decreased ACh turnover (33-51%)
Cahill et al.[277]	Rat	5, 50 ppm in drinking water. 40 day pretreatment of parents continued from conception through adulthood	Normal	180 day 0 = 5 5 = 6 50 = 10	180 day 0 = 18 5 = 20 50 = 27	Steady-state NE, DA	Decreased DA at 28 days of age Increased NE at 180 days of age
Silbergeld and Chisolm[319]	Mouse	5 mg/ml lead acetate in drinking water starting at parturition	Under-nourished	?	?	Brain HVA and VMA	Increased 33 and 48%
Gerber et al.[312]	Mouse	0.1-1000 mg/l lead acetate in drinking water for one year	?	?	?	Steady-state 5HT	No change
Bhatnagar[317]	Rat (200-250 g)	0, 1, 2% lead acetate for 70 days	?	?	?	Tyrosinase activity	No effect
Bull et al.[253]	Rat (200-400 g)	1) 67 μM *in vitro* lead chloride	—	—	—	K+ stimulated respiration of cerebral slices	Inhibition
		2) 3, 12, 60 mg/Pb/Kg total dose over 2 weeks	Impaired growth in 60 mg/kg group	Control = 0.08 3 = 13.2 12 = 72.6 60 = 380	0.06 0.17 0.41 1.02	K+ stimulated respiration of cerebral slices	Inhibited at 12 and 60 mg/kg exposure level
Holtzman and Hsu[320]	Rat	4% lead carbonate at 2 weeks postpartum	Under-nourished, reduced brain weights	?	?	Cerebral and cerebellar mitochondrial respiration	Impaired respiration after 2 weeks of treatment

Abbreviations:
ACh - Acetylcholine
CAT - Choline acetyltranferase
AChE - Acetylcholinesterase
NE - Norepinephrine
DA - Dopamine
5HT - 5-hydroxytryptamine (serotonin)
GABA - Gamma aminobutyric acid
CPK - Choline phosphokinase

Several studies utilizing high levels of lead exposure have reported inhibition of cholinergic function. In a series of experiments on the mouse, Silbergeld et al.[308,309] and Carroll et al.[316] reported decreased potassium-induced release of acetylcholine (ACh) and decreased high-affinity transport of choline. Unfortunately, no control for growth retardation was provided in these experiments and relatively high external exposures to lead were required to produce the effect. This was also true in the rat studies reported by Modak et al.[311] and Shih and Hanin.[315] At lower levels of external exposure, with no accompanying growth retardation, no consistent effects on cholinergic function have been reported (cf. 283 and 318). Thus, if impaired cholinergic function during *in vivo* lead exposure is also found in the absence of undernutrition, and/or growth retardation, which is probable in view of the *in vivo* work reported later in this section, then its relevance to behavioral effects seen at lower exposure levels will need examination.

The effects of lead exposure on catecholamine function have also been extensively studied. Findings have been reported of increased steady-state levels of norepinephrine,[277,307,308] increased activity of monamine oxidase (MAO),[309] increased synaptosomal transport of the precursor tyrosine,[308] and increased amounts of the norepinephrine metabolite, vanillyl mandelic acid, and homovanillic acid in the brain.[319] In studies on steady-state levels of norepinephrine, changes have been reported either in the absence of undernutrition[227] or when values have been compared to pair-fed controls.[307] However, inconsistencies within a given laboratory (cf. 278 vs. 307), absence of similar findings in different laboratories (cf. 283 and 310), and findings of decreased steady-state levels[313] make any conclusions regarding lead-induced changes in noradrenergic systems equivocal. This uncertainty is also found in the reports on dopamine changes following lead exposure (cf. 277, 278, 314 vs. 283, 307, 310).

Human studies attempting to relate subclinical lead exposures to signs of altered brain monoamine function have been initiated utilizing urinary levels of monoamine neurotransmitter metabolites as indices of CNS monoamine turnover rates. Although initial studies on catecholamine excretion have suggested a lead effect, an appended note by Silbergeld and Chisholm[319] indicated difficulty in finding one of the earlier reported effects in subsequent studies. This clinical study again emphasizes some of the problems and uncertainties that have beset investigations of low-level toxicity. Also, as indicated by Wender et al.,[321] urinary metabolites reflect primarily peripheral nervous system activity. In another study[322] altered levels of 5-hydroxyindole acetic acid (5-HIAA) were reported in the urine of occupationally lead-exposed battery factory workers, suggesting possible lead effects on serotonin (5-hydroxytryptamine) systems. No parallel supportive evidence from animal studies has been advanced for such an effect, however, and in fact most reports claim negative findings for any type of measurements of brain serotonin function.[283,308,312-314]

The reasons for the inconsistencies of lead-induced changes in monaminergic and cholinergic functions may be the result in part of interlaboratory differences in dosing regimens and other variations in experimental protocol. One note of caution, however, is appropriate here in that highly variable results are seen within different laboratories, even with the same exposure regimens, assay procedures, etc., from experiment to experiment. This might suggest that some subpopulations of rats or mice might be resistant to lead effects on monoamine transmitters whereas others are more vulnerable, possibly because of genetic factors, subtle variations in diet, etc. More carefully controlled studies in the future that explicity manipulate such variables (genetics, nutrition, etc.) may reveal lead effects even at low exposure levels, given the right circumstances or population segment tested.

Finally, the recent report of Nathanson and Bloom[323] indicated that *in vitro* lead exposure inhibits adenyl cyclase activity (I_{50} = 2.4 μM). This enzyme is responsible for the synthesis of cyclic adenosine 3′,5′-monophosphate (c-AMP) which has been shown to play an important role in the mechanism of action of a number of hormones, including neurotransmitters. The effects of lead exposure on adenyl cyclase and the resultant effects on neurotransmitter systems warrant further investigation.

Several recent reports have dealt with the effects of lead exposure on brain-energy metabolism. Bull et al.[253] reported that both *in vivo* and *in vitro* lead exposure inhibited potassium-stimulated respiration. Of interest was the finding that lower brain levels of lead (approximately 1/30th) were required to inhibit respiration *in vivo* than *in vitro*. Also, these results were seen in animals showing normal growth (12 mg/kg group). Similar findings of inhibited respiration using isolated mitochondria were reported by Holtzman and Hsu[320] and by Brierley.[324]

In contrast to the general lack of consistent effects on steady-state levels of cholinergic substances and associated enzymes, consistent evidence for effects of lead on cholinergic synaptic uptake and release mechanisms have been reported.

More specifically, lead resembles other divalent cations in that it appears to interfere with chemically mediated synaptic transmission as demonstrated by studies of peripheral neural functions. Kostial and Vouk[325] reported that *in vitro* perfusion of the cat superior cervical ganglion with 4.8 μM lead nitrate depressed or blocked nerve transmission. Contraction of the nictitating membrane during acetylcholine perfusion was unaltered. Also, perfusion of the ganglion with excess calcium restored acetylcholine release and thus reversed the lead blockade. From these findings Kostial and Vouk concluded that lead depressed synaptic transmission by impairing acetylcholine release from the presynaptic terminals.

Manalis and Cooper[326] and Cooper and Manalis[327] showed that lead can influence both pre- and postsynaptic events. Using the frog (*Rana ippiens*) sciatic-nerve/sartorius-muscle preparation *in vitro*, they demonstrated that the principal effect of lead was on presynaptic transmitter release, although lead had a weak, curare-like effect on the postsynaptic response to applied acetylcholine. They confirmed the findings of Kostial and Vouk[325] that lead depresses the phasic release of transmitter evoked by nerve stimulation. They further observed that lead increases spontaneous release of acetylcholine as evidenced by increased miniature end-plate potentials (MEPP's). These MEPP's represent the response of the postsynaptic membrane to released acetylcholine in quantities that are insufficient to depolarize the membrane to threshold levels. In a subsequent experiment Kober and Cooper[328] demonstrated that in the frog, lead blocks synaptic transmission in the sympathetic ganglion by competitive antagonism of spike-evoked entry of calcium into the presynaptic nerve terminals with a resultant reduction in acetylcholine release.

Experiments by Silbergeld et al.[329,330] indicated a similar blockade of transmitter release by lead in the rat. Furthermore, they reported a reduced force of contraction in the phrenic-nerve/diaphragm preparation from mice exposed to lead from birth through 60 days of age. The nerve-muscle preparation from these lead-exposed animals showed a reduction in force of contraction with nerve stimulation. Also, a reduced force of contraction was reported upon direct stimulation of the muscle. This observation agrees with the weak postsynaptic effects of lead reported by Manalis and Cooper;[326] but unfortunately, no data were presented by Silbergeld et al.[329,330] on the muscle contraction following electrical stimulation, so the relative importance of this finding cannot be evaluated. Finally, Cooper and Steinberg[331] demonstrated that lead is also capable of blocking neural transmission at the adrenergic synapse. They measured the contraction force of the rabbit saphenous artery following stimulation of the sympathetic nerve endings. Again, the results indicated that lead blocks muscle contraction by an effect on the nerve terminals rather than an effect on the muscle. Since the response recovered when calcium concentration was increased in the bathing solution, it was concluded that lead does not deplete transmitter stores in the nerve terminals but more likely blocks norepinephrine release.

In summary, *in vitro* experiments have demonstrated that lead interferes with synaptic transmission in the peripheral nervous system. This effect appears to be related to a competitive inhibition of calcium-mediated, evoked release of the neurotransmitters. Further, lead was shown to increase the spontaneous release of transmitter from some synapses.

The effects of lead on synapses within the CNS have not been extensively studied. Carroll et al.,[316] however, reported a decrease in potassium-induced release of both choline and acetylcholine from cortical minces of mice chronically exposed to lead. These changes in acetylcholine metabolism suggest that, as is the case of the peripheral nervous system, the central cholinergic function may be depressed by lead. This is further supported by a report of Shih and Hanin[315] that lead exposure decreased *in vivo* acetylcholine turnover rate in cortex, hippocampus, midbrain, and striatum (35, 54, 51, and 33 percent decreases, respectively) in rat brain after neonatal lead exposures. Along with the *in vitro* findings, this provides additional evidence supportive of lead-induced dysfunctions of cholinergic synaptic uptake and release mechanisms. Unfortunately, these results and many from the above peripheral function studies were obtained at rather high exposure levels and most were performed on undernourished or growth-retarded animals.

One final note concerns the relationship between levels of lead in blood and brain. Several studies on rodents have reported simultaneous lead values for blood and brain resulting from lead exposures of various durations. Bornschein et al.[270] exposed mice to 5 mg/ml lead acetate starting at parturition. Brain/blood ratios showed a steady increase from 20 to 100 days of age. Ratios of 1.05, 2.55, and 4.08 were reported for mice at 20, 40, and 100 days of age, respectively. This increase in the brain/blood ratios resulted from both a steady increase in brain lead levels (increasing from 200 μg % at 20 days of age to 584 μg % at 100 days of age) and a decrease in blood lead levels (decreasing from 190 ppm at 20 days to 143 ppm at 100 days).

Cahill et al.[277] reported blood and brain levels of lead in rats exposed from conception to either 0, 5, or 50 ppm lead in the drinking water. At parturition, brain/blood ratios of offspring were 0.91 and 0.5 for exposure levels of 5 and 50 ppm, respectively. At 180 days of age, these ratios were 3.3 and 2.7, respectively. A ratio of approximately 1 was also reported by Grant et al.[310] in 30-day-old rats exposed to various levels of lead from 3 to 25 days of age. These data are consistent with the results of Bornschein et al.[270] and indicate that initially brain/blood ratios are approximately unity but that with continued exposure the ratios steadily increase.

11.5.2.6 SUMMARY AND CONCLUSIONS

Data obtained in laboratory animals, such as that reported in the rat by Pentschew and Garro,[52] indicate that encephalopathy is produced by high-level perinatal exposure to lead. This encephalopathy occurs to varying degrees in different species and is characterized by the relative involvement of neuronal degeneration and vasculopathy.

It seems clear that with regard to CNS toxicity the developing organism represents the population at greatest risk. Whether this increased risk is attributable to a greater sensitivity or to a greater susceptibility of the developing organism will require further testing. That is, with a given external exposure, the CNS of the developing organism reaches a higher concentration of lead and is therefore more susceptible to poisoning. Whether the threshold for a given effect of lead is lower in the immature nervous system versus the adult will need to be determined.

There is also good evidence that perinatal exposure to lead even at moderate exposure levels will produce delays in both neurological and sexual development. Because these effects have been demonstrated to occur in the absence of either undernutrition or growth retardation, it has been suggested that they represent direct effects of lead in the respective organ systems.

In the animal studies, locomotor activity has been the most commonly used behavioral index of lead toxicity. The data reviewed here suggest that perinatal exposure to lead produces an increase in the animal's behavioral reactivity. If the test conditions are appropriate, this increased reactivity will be manifested as increased locomotor activity, although some text situations will show reduced activity. Therefore, the altered activity levels per se are merely reflective of a more basic nervous system dysfunction. Close scrutiny of the available data would also suggest that altered locomotor activity in young animals occurs only at moderately high exposure levels. A comparison of the data of Sobotka and Cook[282] and Overmann[275] are of interest in this regard (see Table 11-4). Using gastric intubation, Overmann reported hyperactivity in young rats whose 21-day blood lead levels were 226 μg/dl. Sobotka and Cook, using a similar exposure regimen, found normal activity levels with 22-day blood lead levels of 71 μg/dl. It appears, therefore, that this early change in reactivity occurs at fairly high blood lead levels. It may be, then, that the changes in activity currently reported in laboratory animals are more representative of a post-encephalopathic hyperactivity than of subclinical effects as has been suggested.

On the other hand, the reactivity changes reported in older animals with lifetime exposure occur at much lower blood levels (cf. 264, 277, and 285).

Finally, reports on the effects of lead exposure on the acquisition and/or performance of operant responses indicate that perinatal exposure to moderate and low levels of lead may disrupt this behavior. Thus, external exposures that result in blood lead levels ranging from 30 to 80 μg/dl have been reported to disrupt cognitive function (see Table 11-5). As is true with the clinical data, this area requires further investigation.

It has been repeatedly indicated that serious methodological problems exist in the animal literature which make it difficult to interpret many of the available data. Future research in this area would benefit from more tightly controlled experiments including:

1. Better documentation of internal exposure, not only with respect to lead levels but also with respect to correlative indices of lead toxicity, e.g., ALAD, protoporphyrin, etc.
2. The use of exposure protocols that do not produce confounding variables such as undernutrition, differences in both litter size and number of litters per treatment group, etc.
3. Validation of behavioral tests using both positive control substances and cross corre-

lation with other physiological indices. This would include research aimed at more closely defining both the relative sensitivity of the CNS compared to other organ systems as well as the contribution of other indirect actions of lead on the resulting behavioral changes.

11.6 EFFECT OF LEAD ON THE RENAL SYSTEM

11.6.1 Acute Effects

More than 60 years ago an English toxicologist, Thomas Oliver,[332] distinguished acute effects of lead on the kidney from lead-induced chronic nephropathy. Acute renal effects of lead are seen in persons dying of acute lead poisoning or suffering from lead-induced anemia and/or encephalopathy and are usually restricted to nonspecific degenerative changes in renal tubular lining cells, usually cloudy swelling, and some degree of cellular necrosis. Cells of the proximal convoluted tubules are most severely affected. As long ago as 1928, Pejie[333] emphasized that the degenerative changes in proximal tubules, rather than the vascular changes often referred to in earlier studies, are primary evidence of injury to the kidney in lead poisoning. Many subsequent studies have shown at least three pathological alterations in the renal tubule with onset during the early or the acute phase of lead intoxication in the kidney. These include the formation of inclusion bodies in nuclei of proximal tubular lining cells and the development of functional as well as ultrastructural changes in renal tubular mitochondria.

Dysfunction of proximal renal tubules (Fanconi's syndrome) is manifested by aminoaciduria, glycosuria, and hyperphosphaturia, and was first noted in acute lead poisoning by Wilson and coworkers in 1953.[334] Plasma amino acids were normal, which suggested that the aminoaciduria and other functional abnormalities were of renal origin. Subsequently, aminoaciduria in children with acute lead poisoning was observed by Marsden and Wilson[335] in England, and Chisholm[85,86] found that 9 of 23 children with lead encephalopathy had aminoaciduria, glycosuria, and hypophosphatemia. Aminoaciduria was seen more consistently in Chisolm's studies than the other two manifestations of tubular damage. Thus, the amino acid transport system is probably more sensitive to the toxic actions of lead than the transport systems for glucose and phosphate. The aminoaciduria was generalized in that the amino acids excreted in greatest amounts were those normally present in urine. The condition was related to severity of clinical toxicity and was most marked in children with encephalopathy. The aminoaciduria disappears after treatment with chelating agents and clinical remission of other symptoms of lead toxicity.[85] This is an important observation relative to the long-term or chronic effects of lead on the kidney.

In a group of children with slight lead-related neurological signs, generalized aminoaciduria was found in 8 of 43 children with blood lead levels of 40 to 120 μg/dl.[99] It should be noted that the children reported to have aminoaciduria in the study of Pueschel[99] were not specifically identified as to their lead exposure. Thus, it is not possible to state what level of lead exposure within the blood lead range of 40 to 120 μg/dl was associated with the effects. A similar renal tubular syndrome has been reported to occur in industrially exposed adults.[336]

11.6.2 Chronic Effects

There is convincing evidence in the literature that prolonged lead exposure in humans[337] can result in chronic lead nephropathy. Cramer et al.[337] in 1974 reported on a group of 7 lead-exposed workers who had been exposed up to 20 years. Aminoaciduria was not found, and inulin clearance and renal blood flow were also reported normal. The average blood lead level was 100 μg/dl, the minimum was 71 μg/dl, and all had strikingly high urinary ALA excretion. Some with very long exposures were reported to have interstitial and peritubular fibrosis, determined by renal biopsy. This pathological finding is commonly referred to as chronic lead nephropathy, which is characterized by slow development of contracted kidneys with pronounced arteriosclerotic changes, fibrosis, glomerular atrophy, and hyaline degeneration of these vessels. This is a progressive disease, sometimes resulting in renal failure. It seems to occur sporadically, primarily in industrially exposed workers and in older adults who have been diagnosed as having lead poisoning early in life. There is also some evidence that it occurs in long-time drinkers of lead-contaminated whiskey, as reported by Morris et al.[338] in the cases of 16 adults treated over a 10-year period. This study reported lead poisoning manifested by the same symptoms found in children. The most specific pathological change reported was the presence of large numbers of acid-fast intranuclear inclusions within the cells of the kidney tubules and liver. Ball and Jorenson[339] reported a high frequency of saturnine gout resulting from the consumption of lead-contaminated whiskey, convincingly demonstrating reduced renal uric acid clearance associated with plumbism.

In a series of 102 cases of lead poisoning studied by Lilis et al.,[340] 18 cases of clinically verified chronic nephropathy were found. For the whole series, the mean blood lead level was approximately 80 μg/dl, with a range of 42 to 141 μg/dl. Nephropathy was more common among patients who had been exposed to lead for more than 10 years than among those who had been exposed for less than 10 years. In both studies, reduced urea clearance preceded reduced creatinine clearance.

In the Danilovic study,[341] 7 of 23 cases had blood lead levels of about 100 to 200 μg/dl. In the studies of Albahary et al.,[342] blood lead levels were not reported but exposure levels must have been quite high because the mean ALA excretion was about 37 mg/24 hr for 29 workers. These studies indicate that the nature of the effect is glomerulovascular, with reduction in clearance of urea and, in more protracted exposures, also of endogenous creatinine. Also, reduced clearance of uric acid was observed in the study of Albahary et al.[342]

In the recently reported studies of Wedeen et al.,[343] eight subjects suspected of excessive occupational exposure were given detailed examinations for renal function. Four of the subjects showed signs of abnormal renal function. In one subject with asymptomatic renal failure, chelation therapy increased the glomerular filtration rate, the *p*-amino hippurate (PAH) extraction, and the maximal PAH excretion rate, and improved the proximal tubule ultrastructure, despite decreased renal plasma flow. Three of the subjects showed proximal tubule abnormalities via biopsy. In eight subjects, lead-induced nephropathy was established by exclusion. The blood lead values of the individuals ranged from 48 μg/dl, for the subject having asymptomatic renal failure, to 98 μg/dl. The lead levels of the other two subjects in the preclinical renal dysfunction category were 51 and 66 μg/dl. All subjects showed glomerular filtration rates of less than 87 ml/min/1.73m^2. The authors suggest on the basis of these studies that lead nephropathy may be an important occupational hazard in the U.S. lead industry.

A series of reports from Queensland, Australia,[344] points to a strong association between severe lead poisoning in childhood including central nervous system symptoms and chronic nephritis in early adulthood. Henderson[345] followed up 401 children who had been diagnosed as having lead poisoning in Brisbane between 1915 and 1935. Of these 401 subjects, 165 had died, 108 from nephritis or hypertension. This is greatly in excess of expectation. Information was obtained from 101 of the 187 survivors, and 17 of these had hypertension and/or albuminuria. In a more recent study, Emmerson[346] presented a criterion for implicating lead as an etiological factor in such patients: the patients should have an excessive urinary excretion of lead following administration of calcium EDTA. In his study, 32 patients with chronic renal disease attributable to lead poisoning had similarly elevated excretion of lead. The presence of intranuclear inclusion bodies is very helpful in establishing a relationship between renal lesions and lead toxicity, but inclusion bodies are not always present in persons with chronic lead nephropathy.

Attempts to confirm the relationship between childhood lead intoxication and chronic nephropathy have not been successful in at least two studies in the United States. Tepper[90] found no evidence of chronic renal disease in 42 persons with a well-documented history of childhood plumbism 20 to 35 years earlier at the Boston Children's Hospital. Likewise, Chisolm[347] found no evidence of renal disease in 62 adolescents known to have had lead intoxication 11 to 16 years earlier. An important distinction between the Australian group and patients in the United States was that none of Chisholm's[347] subjects showed evidence of increased residual body lead burden following the EDTA mobilization test. This difference has suggested to Chisholm that lead toxicity in the Australian children must have been of a different type, with a more protracted course than that experienced by the American children. Most children in the United States who suffer from lead toxicity do so early in childhood, between the ages of 1 and 4, the source usually being oral ingestion of flecks of wall paint and plaster containing lead.

11.7 REPRODUCTION AND DEVELOPMENT

As reviewed thus far in the present chapter, the adverse effects of lead on the hematopoietic, nervous, and renal systems have been well documented across a wide range of exposure levels and represent a triad of symptoms classically associated with lead poisoning. Extensive evidence for adverse effects of lead on reproduction and development has also been accumulating in the literature for many years and has become a matter of increasing medical concern. Data from both human and animal studies indicate that lead exerts gametotoxic, embryotoxic, and, possibly, teratogenic effects that impact on the pre- and postnatal survival and development of the fetus and newborn, respectively. In addition, it appears that the viability and development of the fetus may also be markedly affected by lead indirectly via adverse effects on various health parameters, e.g., nutritional state or blood chemistry, of the expectant mother. The vulnerability of the fetus to such lead effects while *in utero* has contributed to concern that pregnant women may be a special group at risk for lead poisoning. Certain information on adverse lead effects on male reproductive functions, it should also be noted, has led to additional concern regarding the impact of lead on men.

11.7.1 **Human Studies**

Data suggesting that lead exerts adverse effects on human reproductive functions have existed in the literature since before the turn of the century. For example, Legge,[348] in summarizing the reports of 11 English factory inspectors in 1897, found that of 212 pregnancies in 77 female lead workers only 61 living children were produced. Fifteen workers had never become pregnant. There were 21 stillborns, miscarriages occurred 90 times, and, of 101 children born, 40 died in the first year. Legge also noted that when pregnant animals were fed lead they always aborted. He concluded that maternal exposure to lead resulted in a direct action of the element on the fetus.

In 1911, Oliver[180] published statistics in Britain on the effect of lead on pregnancy (Table 11-10) which showed that the miscarriage rate was elevated among women employed in industries in which they were exposed to lead.

TABLE 11-10. STATISTICS ON THE EFFECT OF LEAD ON PREGNANCY[180]

Sample	Number of abortions and stillbirths per 1000 females	Number of neonatal deaths (first year) per 1000 females
Housewives	43.2	150
Female workers (mill work)	47.6	214
Females exposed to lead premaritally	86.0	157
Females exposed to lead after marriage	133.5	271

Since the time of the above studies, women have been largely excluded from occupational exposure to lead. Even before the effects of industrial lead exposure on pregnancy were documented, however, lead compounds were known for their embryotoxic properties and were often used to induce criminal abortion.[349] In a study by Lane,[350] women exposed to lead levels of 75 $\mu g/m^3$ were examined for effects on reproduction. Longitudinal data on 15 pregnancies indicated an increase in the number of stillbirths and abortions. No data were given on urinary lead in women, but men in this sample had urinary levels of 75 to 100 μg/liter.

In a more recent study[351] of the pregnancies of 104 Japanese women married to lead workers before and after their husbands began lead work, miscarriages increased to 84.2/1000 pregnancies from a prelead rate of 45.6/1000. The miscarriage rate for 75 women not exposed to lead was 59.1/1000.

Another recent study by Fahim et al.[352] in humans suggests that subtoxic lead absorption during pregnancy may be associated with an increased incidence of preterm delivery and early membrane rupture: 253 women delivered in Rolla, Missouri (Region I), which is 60 to 80 miles from lead smelters, and 249 women delivered in Columbia, Missouri (Region II), where there is no lead industry. The incidence of term pregnancies with early membrane rupture was 17 percent in Region I and 0.41 percent in Region II. The incidence of premature deliveries was 13.04 and 3 percent, respectively. A high correlation was found between lead concentrations in maternal and fetal blood: both were significantly higher in the cases of preterm pregnancies and early membrane ruptures than in term pregnancies.

Pregnancy is a stress that may place a woman at higher risk for lead exposure. Both iron deficiency and calcium deficiency increase the susceptibility of lead toxicity, and women have an increased risk of both deficiencies during pregnancy and postpartum. The cause of the increased perinatal mortality may be a mutagenic or teratogenic effect of lead.[353]

The above studies clearly demonstrate an adverse effect of lead on human reproductive functions, ranging from reduced pregnancy rates to increased incidence of miscarriages, premature deliveries, and stillbirths. The mechanisms underlying these effects are unknown at this time. Many factors could contribute to the above results, ranging from lead effects on maternal nutrition or hormonal state before or during pregnancy to more direct gametotoxic, embryotoxic, or teratogenic effects that could affect fertility or fetal viability during gestation. Efforts have been made to define more precisely the points at which lead may affect reproductive functions both in the human female and male, and in other animals, as reviewed below.

In regard to potential lead effects on ovarian function in human females, Panova[354] reported a study of 140 women working in a printing plant for less than 1 year (1 to 12 months) where ambient air levels were <7 μg lead/m^3. Using a classification of various age groups (20 to 25, 26 to 35, and 36 to 40) and type of ovarian cycle (normal, anovular, and disturbed lutein phase), Panova claimed that statistically significant differences existed between the lead-exposed and control groups in the age range of 20 to 25 years. It should be noted that the report does not show the age distribution, the level of significance, or the data on specificity of his method of classification. Also, Zielhuis and Wibowo,[355] in a critical review of the above study, concluded that study design and presentation of data are such that it is difficult to evaluate the author's conclusion that chronic exposure to low lead in air leads to a disturbed function of ovaries. It should be noted that no consideration was given to the dust levels of lead, an important factor in print shops.

Unfortunately, little else besides the above report exists in the literature in regard to assessing lead effects on ovarian function or other factors affecting human female fertility. Nor are there many studies offering firm data on maternal variables, e.g., hormonal state, that are known to affect the ability of the pregnant woman to carry the fetus full term. In addition, there are no studies that demonstrate conclusively a direct lead-induced teratogenic effect on the human fetus, although the transfer of lead across the human placenta and its potential threat to the conceptus have been recognized for more than a century.[356] Nevertheless, documentation of placental transfer of lead to the fetus and data on relevant parameters, e.g., fetal blood lead levels resulting from such transfer, help to build the case for a potential, but as yet not clearly defined, threat for subtle teratogenic and other deleterious health effects.

The placental transfer of lead has been established, in part, by various studies that have disclosed measurable quantities of lead in human fetuses or newborns. An analysis of human fetal tissues by Barltrop[357] demonstrated that placental transfer of lead began as early as the 12th week of gestation and that total lead content increased throughout fetal development, with the highest concentrations occurring in bone, kidney, and liver, and lesser, but significant, amounts occurring in blood, brain, and heart. Barltrop has also pointed out that the distribution of lead within the fetus at different stages of development is probably more important than the total amount present at birth.

Of interest in this regard are the data of Schroeder and Tipton,[358] who showed that the mean lead level in brains of stillborn U.S. children (n = 22) was 10 ppm (dry ash), but that there was an undetectable level for normal infants, young children, and teens (0 to 19 years; n = 23). In this study, however, the levels of detection are not stated, so that the relative increase in level cannot be assessed. Also, it is not clear to what extent fetal tissue preparation and preservation were controlled for contamination.

Wibberly and coworkers[359] have recently found that placental lead levels in the case of stillbirth or neonatal death were significantly higher than in the case of normal births. Placental levels were greater than 1.5 μg/g in only 7 percent of the normal births, whereas levels were greater than this in 61 percent of the stillbirths or neonatal deaths. This does not mean that lead is a causal factor in such deaths and could indicate that lead accumulates in the placenta in times of fetal stress.

There are a number of recent studies on the passage of lead through the placental barrier as assessed by lead levels in cord blood and/or maternal blood. For example, in the study of Gershanik et al.,[360,361] 98 cord-blood samples matched with maternal blood samples showed a high correlation between lead levels in infants (mean = 10.1 μg/dl) and their mothers (mean = 10.3 μg/dl), with a product moment correlation coefficient of 0.6377. This suggests that infants may be born with blood lead levels that essentially match those of their mothers. In regard to assessing groups at risk for such prenatal exposure, these authors also studied a group of 218 cord-blood samples (170 urban, 48 rural) and observed that the mean urban value (9.7 μg/dl) was significantly different ($p < 0.05$) from the mean rural value (8.3 μg/dl), suggesting a higher risk of urban newborns for prenatal lead exposure. Similarly, Scanlon[362] sampled cord-blood randomly from normal infants whose mothers had suburban (n = 15) or urban (n = 13) residences. The average urban value was 22.1 μg/dl (10 to 37 μg/dl), whereas the corresponding suburban level was 18.3 μg/dl. Smoking was without significant effect on these levels. These results tend to confirm the findings of Gershanik et al.[361] Harris and Holley,[363] on the other hand, surveyed cord and maternal blood in 24 pairs (11 suburban and 13 urban) and found a mean cord-blood value of 12.3 μg/dl and a mean maternal blood level of 13.2 μg/dl. No significant difference was therefore seen in cord-blood levels as a function of maternal residence, though a larger sample might have yielded significant effects since the ones found were in the same direction as those found in other studies.

That the prenatal exposure of the fetus to lead, even in the absence of teratogenic effects, may be of consequence in regard to adverse health effects is demonstrated by studies relating fetal and cord-blood levels to some changes in fetal heme synthesis and claimed incidences of premature births. Haas et al.[364] examined 294 mother-infant pairs for blood lead levels as well as for the corresponding urinary ALA levels. The maternal blood mean was 16.89 μg/dl and the fetal blood mean was 14.98, with a correlation of 0.538 ($p < 0.001$). In the infants, the levels of blood lead and urinary ALA were positively correlated ($r = 0.1877$, $p < 0.01$). Whether a biological significance exists here, however, is not clear. According to the authors,[364] the positive correlation between lead in blood and urinary ALA for the group as a whole indicated there was already an effect at lower blood lead levels, i.e., increased susceptibility of heme synthesis.

In a study of Fahim[365] on cord-blood lead levels, blood lead values in pregnant women having preterm delivery and premature membrane rupture, and residing in a lead belt area (mining and smelting area), had significantly higher blood lead levels than women delivering at full term. A confusing aspect of this study, however, is the similarity of blood lead levels in women in the nonlead and lead belt areas. Though a number of other problems may be seen with the analytical aspects of this study, it must be noted that among the 249 pregnant women in the control group outside the lead belt area the percentage of women having preterm deliveries and premature rupture were 3 and 0.4 percent, respectively, whereas the corresponding values for the lead area ($n = 253$) were 13.04 and 16.99 percent, respectively.

With reference to more subtle prenatal effects, Palmisano et al.[366] noted failure to thrive and neurological deficits in a 10-week-old infant whose mother had lead poisoning concomitant with alcoholism during pregnancy. When this infant was challenged with a chelating agent, an abnormal urinary excretion of lead was observed, indicating intrauterine exposure. Postnatal exposure in this case was ruled out. Other, more controlled laboratory studies on animals (discussed later) also suggest that teratogenic effects occur, but usually only at very high lead exposure levels.

A report[367] on fatal birth defects in children conceived during a period of time when their father was lead poisoned hints at important effects of lead on the fetus being mediated via human males as well as females. Certain other studies[369,370] demonstrated likely lead effects on various aspects of male reproductive functions.

Lancranjan et al.[368] have reported that moderately increased lead absorption (blood lead mean = 52.8 μg/dl) resulted in gonadal impairment. The effects on the testes were shown to be direct in that tests for hypothalamopituitary influence were negative. A group of 150 workmen who had long-term exposure to lead in varying degrees was studied. Clinical and toxicological criteria were used to categorize the men into four groups: lead-poisoned workmen (74.5 μg/dl) and those showing moderate (52.8 μg/dl), slight (41 μg/dl), and physiologic (23 μg/dl) absorption of lead. Semen analysis revealed asthenospermia, hypospermia, and teratospermia in lead-poisoned workers and those with moderately increased absorption of lead (blood lead levels = 50 to 80 μg/dl for the latter). The abnormal spermatozoa included binucleated, bicephalus, amorphous, and tapered forms. In contrast, slightly increased or physiologic absorption of lead had no effects on the reproductive ability of workmen.

In the review of Stöfen,[369] data from the work of Neskov in the USSR were reported involving 66 workers exposed chiefly to lead-containing gasoline (organic lead). In 58 men there was a decrease or disappearance of erection, in 41 there was early ejaculation, and in 44 there was a diminished number of spermatocytes.

The literature reviewed here on lead effects on human reproduction and development leaves little doubt as to the fact that lead does, in fact, exert significant adverse health effects on reproductive functions. Most studies, however, have typically looked at the effects of prolonged moderate-to-high exposures to lead, e.g., those encountered in industrial situations, and many reports do not provide definite information on external exposure levels or blood lead levels at which specific effects are observed.

11.7.2 Animal Studies

Animal experiments have demonstrated that levels of lead that are compatible with life have interfered with normal reproduction. Many studies assessed the effects of lead exposure of both parents on reproduction. Schroeder and Mitchener,[370] for example, showed a reduction in the number of offspring of rats and mice that were given drinking water containing lead in a concentration of 25 ppm. In a subsequent report,[371] however, it was noted that animals in the earlier study were chromium deficient. No effects were found in animals with normal diets. The combined effect of maternal and paternal oral lead intoxication upon reproductive performance was studied in rats by Morris et al.[372] who reported significant reduction in weaning percentage among offspring of rats fed 512 ppm lead. Stowe and Goyer[373] assessed the relative paternal and maternal effects of lead as measured by the progeny of F_1 lead-toxic rats. Sprague-Dawley female rats being fed laboratory chow with and without 1 percent lead acetate were bred to normal, mature, Sprague-Dawley males. The pregnant rats were continued on their respective rations with and without lead throughout gestation and lactation. Offspring of these matings, the F_1 generation, were fed the rations of their dams and were mated in combinations as follows: control female to control male (CF-CM), control female to lead-toxic male (CF-PbM), lead-toxic female to control male (PbF-CM), and lead-toxic female to lead-toxic male (PbF-PbM). The results identifying specific deleterious paternal and maternal effects of lead toxicity upon rat reproduction are shown in Table 11-11.

TABLE 11-11. REPRODUCTIVE PERFORMANCE OF F_1 LEAD-TOXIC RATS[373]

Parameter	Type of mating			
	CF-CM	CF-PbM	PbF-CM	PbF-PbM
Litters observed	22	24	36	16
Pups/litter	11.90 ± 0.40[a]	10.10 ± 0.50	8.78 ± 0.30[b]	7.75 ± 0.50[c]
Pup birth weight, g	6.74 ± 0.15	5.92 ± 0.13[c]	5.44 ± 0.13[c,d]	4.80 ± 0.19[c,d,e]
Weaned rats/litter	9.84 ± 0.50	7.04 ± 0.77[c]	5.41 ± 0.74[c,d]	2.72 ± 0.70[c,d,e]
Survival rate, %	89.80 ± 3.20	73.70 ± 7.90	52.60 ± 7.20	30.00 ± 8.20[c,d,f]
Litter birth weight/Dam breeding weight, %	28.04 ± 1.30	22.30 ± 0.90[c]	19.35 ± 1.00[c]	15.38 ± 1.10[c,d,f]
Litter birth weight/Dam whelping weight, %	19.09 ± 0.80	15.97 ± 0.58[c]	14.28 ± 0.66[c]	11.58 ± 0.78[c,d,f]
Gestation gain/Pups per litter, g	11.54 ± 0.60	11.20 ± 0.74	11.17 ± 0.54	12.34 ± 1.24
Nonfetal gestational/Gain/fetus, g	3.93 ± 0.38	4.83 ± 0.47	4.15 ± 0.42	3.96 ± 0.46

[a] Mean ± S.E.M
[b] Significantly ($p < 0.05$) less than mean for CF-CM.
[c] Significantly ($p < 0.01$) less than mean for CF-CM.
[d] Significantly ($p < 0.01$) less than mean for CF-PbM.
[e] Significantly ($p < 0.01$) less than mean for PbF-CM.
[f] Significantly ($p < 0.05$) less than mean for PbF-CM.

The paternal effects of lead included a 15 percent reduction in the number of pups born per litter, a 12 percent reduction in the mean pup birth weight, and an 18 percent reduction in pup survival rate. The maternal effects of lead included a 26 percent reduction in litter size, 19 percent reduction in mean pup birth weights, and 41 percent reduction in pup survival. The combined male and female effects of lead toxicity resulted in 35 percent reduction in the number of pups per litter, 29 percent reduction in the pup birth weights, and 67 percent reduction in pup survival to weaning. Stowe and Goyer[373] classified the effect of lead upon reproduction as gametotoxic, intrauterine, and extrauterine. The gametotoxic effects of lead appear to be irreversible and had additive male and female components. The intrauterine effects resulted from the transmammary passage of lead from the dam to the suckling pup adding insult to the gametotoxic and uterine environmental effects.

The effects of lead on the reproduction of sexually mature male and female Sesco rats were reported by Hildebrand et al.[374] The animals were orally fed lead acetate at doses of 5 and 100 μg for 30 days. Control females possessed the same levels of lead concentration in their blood as those for male controls. However, for the treated animals the blood lead levels for the females were higher than those for the males: 30 μg/dl versus 19 μg/dl at 5 μg lead acetate, and 53 μg/dl versus 30 μg/dl at 100 μg lead acetate. They noted impotence and prostatic hyperplasia in the males at the lower dose, progressing to testicular damage with inhibition of spermatogenesis in those reaching blood levels of 50 μg/dl. In the females, they noted irregularity of the estrus cycle at both doses. When lead levels reached 50 μg/dl, the female rats developed ovarian follicular cysts with a reduction in the number of corpora lutea. A subsequent study employing Sprague-Dawley rats was unable to replicate these findings.[375]

A number of other studies have focused more specifically on either maternal or paternal lead exposure effects. For example, in reference to maternal effects, histopathological changes in ovaries in lead-poisoned Rhesus monkeys have been demonstrated.[376] Most other animal studies have utilized rodents.

Kennedy et al.[377] administered an aqueous solution of lead to mice (days 5 to 15 of gestation) and to rats from days 6 to 16 of gestation. At dosage levels of 7.14, 71.4, and 714 mg/kg body weight there were no observed effects on the number of fetuses resorbed or the number of viable fetuses. No teratogenic effects on gross examination were seen, and an effect on body weight was observed only at the highest level employed (714 mg/kg).

Hubermont et al.[378] exposed female rats to lead in drinking water (0.1, 1, and 10 ppm) for 3 weeks before mating, during pregnancy, and 3 weeks after delivery. In the highest exposure group (10 ppm), maternal and newborn blood and kidney lead values were elevated. Inhibition of δ-ALAD and elevation of FEP in tissues were also noted.

Maisin et al.[379] exposed female mice to lead in the diet (0.1 and 0.5 percent) from the day of vaginal plug to 18 days afterwards. The number of pregnancies decreased and the number of embryos succumbing after implantation increased.

Similarly, Jacquet[380] exposed female mice via lead in diet (0.125, 0.25, and 0.50 percent) from vaginal plug to 16 to 18 days afterwards. At the middle dosage, pregnancy incidence decreased, the number of embryos dying before implantation increased, and the number of corpora lutea showed a decrease. At the highest dosage, the number of embryos dying after implantation increased, whereas decreases in body weight of surviving embryos were seen.

Other studies have focused on lead effects on paternal reproductive functions. For example, the data from studies of rabbits,[381] guinea pigs,[382] and rats[373,383] indicate that paternally transmitted effects from lead can occur, including reductions in litter size, in weights of offspring, and in survival rate.

Cole and Bachhuber,[381] using rabbits, were the first to confirm experimentally the paternal effects of lead intoxication. The litters of dams sired by lead-toxic male rabbits were smaller than those sired by control males. Weller[382] similarly demonstrated reduced birth weights and survival among offspring of lead-toxic male guinea pigs.

Verma et al.[384] fed a 2-percent aqueous solution of lead subacetate in drinking water to 14 male Swiss mice for 4 weeks. The total mean intake of lead amounted to 1.65 g. They placed the male with 3 virgin untreated females for 1 week. The overall incidence of pregnancy, indicative of fertility, was 52.7 percent in the control group as compared to 27.6 percent in the treated group. The fertility of the treated males was reduced to 50 percent. They calculated the mutagenicity index (number of early fetal deaths/total implants) to be 10.4 for lead-treated mice versus 2.9 for controls ($X^2 = 10.4$, $p \le 0.05$).

In the study of Maisin et al.,[379] male mice received 0.1 and 1 percent lead, as the acetate, in the diet. The percentage of abnormal spermatozoa increased with increasing exposure. Ultrastructural changes were present.

In the review of Stöfen,[369] several studies from Russian laboratories were evaluated. As cited by Stöfen, Egorova et al., for example, injected lead at a dose of 2 μg/kg 6 times over a 10-day period and observed damage to testes and spermatozoa. Stöfen also reported that Golubova et al. found morphological changes in testes of rats that received 2 mg lead/kg but not in rats receiving 0.2 mg/kg.

Lead appears to be teratogenic in some species, at least at high exposure levels. McClain and Becker,[385] for example, administered single doses of 25 to 70 mg/kg of lead nitrate intravenously to pregnant rats on days 8 through 17 of gestation. A urorectocaudal syndrom of malformations was produced when lead was administered on the 9th day of gestation. The lead nitrate was increasingly embryo- and fetotoxic when administered on later days of gestation (days 10 to 15) but not teratogenic. Ferm and Carpenter[386] as well as Ferm and Ferm[387] reported increased embryonic resorption and malformation rates when various lead salts were administered to pregnant hamsters on the 8th day of gestation. The teratogenic effect of lead was almost completely restricted to the tail region. Malformations of the sacral and caudal vertebrae, resulting in absent or stunted tails, were observed.

The reasons for the localization of the teratogenic effects of lead are unknown at this time. Ferm and Ferm[387] have suggested that the specificity could be explained by an interference with specific enzymatic events during early development. Lead alters mitochondrial function and enhances or inhibits a variety of enzymes,[388] any or all of which could interfere with normal development. Ferm[389] has also reported that in the presence of cadmium the teratogenic effect of lead in hamsters is potentiated.

Studies by Giliani[390,391] show that lead is teratogenic to chick embryos. When 2-day-old embryos were given varying doses of lead acetate (0.005 to 0.08 mg/egg) and were examined on the

8th day of incubation, congenital cardiac anomalies were demonstrated.[390] The incidence of cardiac anomalies rose with increasing doses of lead. Other important anomalies were reduced body size, micromelia, shortened neck, microophthalmia, ruptured brain, shortened beak, twisted neck and limbs, and everted viscera.[391] The most common developmental anomalies were retarded growth and neck abnormalities. It should be noted that in these studies high, acute doses of lead were administered.

There is a paucity of information regarding the teratogenicity and developmental toxicity of chronic lead exposure. Kimmel et al.[265] exposed female rats chronically to lead acetate via drinking water (0.5, 5, 50, and 250 μg/g) from weaning through mating, gestation, and lactation. No teratogenic effects were observed, although exposure to 250 μg/g lead acetate caused a slight but nonsignificant increase in fetal resorptions. The lead-treated animals produced litters of normal numbers, but the offspring from the 50- and 250-μg/g groups weighed less at weaning and showed delays in physical development. Reiter et al.[264] have also observed delays in the development of the nervous system in offspring exposed to 50 μg/g lead throughout gestation and lactation. Whether these delays in development result from a direct effect of lead on the nervous system of the pups or reflect secondary changes (resulting from malnutrition, hormonal inbalance, etc.) is not clear. Whatever the mechanisms involved, these studies suggest that low-level, chronic exposure to lead may induce postnatal developmental delays in rats.

It should be noted that the above reports on normal developmental delays might be analogous to certain suggested neurobehavioral effects of lead from *in utero* exposures of humans (Section 11.5). In addition, it has been demonstrated[392] that concentrations of lead of approximately 170 μg/dl whole blood can inhibit δ-ALAD activity in both blood and brain of suckling rats. Although brain tissue was not purged of residual blood, ALAD contribution to brain ALAD activity would not be expected to be significant. It is possible that δ-ALAD activity might be diminished *in utero* at these lead levels and that lead at these levels might have harmful consequences on neurological development of the fetus. There is need for more critical research to evaluate the possible subtle toxic effects of lead to the fetus. This overall evaluation in the offspring may need to be correlated with the possible additive effects of paternal lead burden. At this time, however, insufficient evidence exists to allow for firm statements on exposure levels at which any such effects on the fetus from maternal or paternal lead burdens might be observed.

11.8 THE ENDOCRINE SYSTEM

The endocrine effects of lead are not well defined at the present time. Lead is known, however, to decrease the thyroid function in man and experimental animals. Porritt[393] suggested in 1931 that lead dissolved from lead pipes by soft water was the cause of hypothyroidism in individuals living in southwest England. Later, Kremer and Frank[394] reported the simultaneous occurrence of myxedema and plumbism in a house painter. Monaenkova[395] in 1957 observed impaired concentration of ^{131}I by thyroids in 10 out of 41 patients with industrial plumbism. Subsequently, Zel'tser[396] showed that *in vivo* ^{131}I uptake and thyroxine synthesis by rat thyroid were decreased by lead when doses of 2 and 5 percent lead acetate solution were administered. Uptake of ^{131}I, sometimes decreased in men with lead poisoning, can be offset by treatment with thyroid-stimulating hormone (TSH).[397,398] Lead may act to depress thyroid function by inhibiting SH groups or by displacing iodine in a protein sulfonyl iodine carrier,[397] and the results suggest that excessive lead may act at both the pituitary and the thyroid gland itself to impair thyroid function.

Sandstead et al.[399] studied the effects of lead intoxication on the pituitary and adrenal function in man. There was a decrease in secretion of pituitary gonadotrophic hormones. Their data suggested that lead may interfere with pituitary function in man and may produce clinically significant hypopituitarism in some. Its effects on adrenal function were less consistent, but some of the patients showed a decreased responsiveness to an inhibitor (metapyrone) of 11-beta-hydroxylation in the synthesis of cortisol.

Excessive oral ingestion of lead in man has resulted in pathological changes in the pituitary-adrenal axis as indicated by decreased metapyrone responsiveness, a depressed pituitary reserve, and decreased immunoreactive ACTH.[400,401] These same events may also affect adrenal gland function inasmuch as decreased urinary excretion of 17-hydroxycorticosteroids was observed in these patients.

Suppression of responsiveness to exogenous ACTH in the zona fasciculata of the adrenal cortex has been reported in lead-poisoned subjects,[402] and impairment of the zona glomerulosa of the adrenal cortex has also been suggested.[403]

There also is some evidence suggesting that lead may cause a derangement in serotonin metabolism or utilization. Tryptophan is the precursor of the neuroendocrine regulatory amine, serotonin. An effect of lead on serotonin synthesis or utilization is inferred in part from the observation of Urbanowicz et al.[404] who reported a rise in 5-hydroxyindole acetic acid (5-HIAA) excretion in the urine of workers heavily exposed to lead. This rise preceded the rise in urinary δ-ALA and coproporphyrin. A similar rise in 5-HIAA excretion was noted in moderately lead-exposed workers.[322] More recently, however, Schiele et al.,[405] using a different analytical method, were unable to find any significant elevation in 5-HIAA excretion.

11.9 THE HEPATIC SYSTEM

The effect of lead poisoning on liver function has not been extensively studied. In a laboratory study of 301 workers in a lead smelting and refining facility, Cooper et al.[406] found serum glutamic oxalacetic transaminase (SGOT) activity at an increased value of 11.5 percent in subjects with blood lead levels below 70 μg/dl, 20 percent in those with a blood lead level of about 70 μg/dl, and 50 percent in workers with a blood lead level of about 100 μg/dl. The correlation between blood lead levels and SGOT was not statistically significant. In the absence of information on the possible influence of diet, infection, or personal habits, however, the authors were unable to draw any definite conclusions concerning the etiology of these changes.

The liver is the major organ for the detoxification of drugs. In acute lead poisoning, the mixed-function oxidase system of liver endoplasmic reticulum is impaired.[407] The activity of this enzyme system, involved in the hepatic biotransformation of medicaments, hormones, and many environmental chemicals, is closely related to the availability of the microsomal hemoprotein, cytochrome P-450.[408] It has been shown that in rats lead induces inhibition of heme synthesis and, therefore, causes a reduction in cytochrome P-450 levels, with consequent impairment of the mixed-function oxidase system.[409] Drug-metabolizing activities were significantly decreased in the lead-poisoned animals. Intensity and duration of these changes were dose dependent. *In vivo* experiments, based on the duration of pentobarbital sleeping time, provided further evidence for the inhibition of drug metabolism in lead-poisoned rats. These data would suggest than an enhanced sensitivity to xenobiotics (drugs, pesticides, food additives, etc.) should be expected to occur in lead-poisoned animals. Alvarez et al.[410] studied the effect of lead exposure on drug metabolism in children and adults. There were no differences between two normal children and eight lead-poisoned children in their capacities to metabolize two test drugs, antipyrine and phenylbutazone. This might suggest that low plasma concentrations of lead do not have an effect on the hepatic cytochrome P-450-dependent enzymatic activities in children. In 2 acutely poisoned children, in whom plasma levels of lead exceeded 60 μg/dl, antipyrine half-lives were significantly longer than normal, and therapy with EDTA led to biochemical remission of the disease and restoration of deranged drug metabolism toward normal.

Hepatic drug metabolism in eight adult patients showing marked effects of chronic lead intoxication on the erythropoietic system was studied by Alvarez et al.[411] The plasma elimination rate of antipyrine, which, as noted above, is a drug primarily metabolized by hepatic microsomal enzymes, was determined in eight subjects prior to and following chelation therapy. In seven of eight subjects, chelation therapy shortened the antipyrine half-lives, but the effect was minimal. The two authors concluded that chronic lead exposure results in significant inhibition of the heme biosynthetic pathway without causing significant changes in hepatic cytochrome P-450-associated enzymatic activities.

11.10 THE CARDIOVASCULAR SYSTEM

Under conditions of long-term exposure at high levels, arteriosclerotic changes have been demonstrated in the kidney. In 1963, Dingwall-Fordyce and Lane[82] reported a marked increase in the cerebrovascular mortality rate among heavily exposed lead workers as compared with the expected rate. These workers were exposed to lead during the first quarter of this century when working conditions were quite bad. There was no similar increase in the mortality rate for men employed more recently.

Hypertension is an important element in the etiology of cerebrovascular deaths. Tabershaw and Cooper[412] did an epidemiological study of 1267 workers who had been exposed to lead as a result of their occupation in either the battery or lead smelting industry between 1947 and 1970. Many were found to have blood lead concentrations in excess of 80 μg/dl. The authors concluded that there was excess mortality associated with only two categories of illness, chronic nephritis and hypertension. The increased incidence of hypertension in lead workers has also been reported by Monaenkova and Glotova[413] and Vigdortchik.[414] On the other hand, Cramer and Dahlberg[415] studied the incidence of hypertension in a population of 364 industrially exposed men, 273 of whom had a long-term exposure to lead. They subdivided the workers into lead-affected and nonlead-affected groups based on the urinary coproporphyrin test. There was no statistically significant difference between the groups nor was the incidence higher than that expected for nonexposed men in the general population. Other reports on the question do not show hypertension to be unduly prevalent among lead workers.[350,416] It is not clear, therefore, whether the vascular effects of lead in man are direct effects on blood vessels or whether the effects are secondary to renal effects.

There are conflicting reports regarding whether lead can cause atherosclerosis in experimental animals. Sroczynski et al.[417] observed increased serum lipoprotein and cholesterol, and cholesterol deposits in the aortas of rats and rabbits receiving large doses of lead. On the other hand, Prerovska,[418] using similar doses of lead given over an even longer period of time, did not produce atherosclerotic lesions in rabbits.

Structural and functional changes of the myocardium have been noted in children with acute lead poisoning, but, to date, the extent of such studies has been very limited. Cases have been described in adults and in children, always with clinical signs of poisoning. There is, of course, the possibility that the coexistence of lead poisoning and myocarditis is coincidental. In many cases in which encephalopathy is present, the electrocardiographic abnormalities disappeared with chelation therapy, suggesting that lead may have been the original etiological factor.[419-421] Silver and Rodriguez-Torres[421] noted abnormal electrocardiograms in 21 of 30 children (70 percent) having symptoms of lead toxicity. After chelation therapy, the electrocardiograms remained abnormal in only four (13 percent) of the patients. Electron microscopy of the myocardium of lead-intoxicated rats has shown diffuse degenerative changes.[422] In a review of five fatal cases of lead poisoning in young children, degenerative changes in heart muscle were reported to be the proximate cause of death.[91] It is not clear that such morphological changes are a specific response to lead intoxication. Kosmider and Petelnz[423] examined 38 adults over 46 years of age with chronic lead poisoning. They found that 66 percent had electrocardiographic changes, which was 4 times the expected rate for that age group.

Makasev and Krivdina[424] observed a two-phase change in the permeability of blood vessels (first, increased permeability; second, decreased permeability) in rats, rabbits, and dogs that received a solution of lead acetate. A phase change in the content of catecholamines in the myocardium and in the blood vessels was observed in subacute lead poisoning in dogs.[425] This effect appears to be a link in the complex mechanism of the cardiovascular pathology of lead poisoning.

11.11 THE IMMUNOLOGIC SYSTEM

Recent reports suggest that exposure to lead may interfere with normal susceptibility to infection. Hemphill et al.[426] found that mice injected with subclinical doses of lead nitrate for 30 days showed greater susceptibility to challenge with *Salmonella typhimurium* than controls that received a saline injection containing no lead. Selye et al.[427] found that rats injected with lead acetate (minimal effective dose of 1 mg/100 g body weight) were susceptible to a variety of bacterial endotoxins (toxins produced by the bacteria themselves) to which this species is ordinarily resistant. Administration of lead acetate in drinking water to male mice from 4 weeks of age to sacrifice at 9 to 12 weeks old increased the toxic response of the mice to 5 classes of viruses against which it was tested.[428,429] These viruses were an RNA picornavirus (encephalomyocarditis), a DNA herpesvirus (pseudorabies), an RNA leukemia virus (Rauscher leukemia), and RNA arbovirus B (St. Louis encephalitis), and an RNA arbovirus A (western encephalitis).

Among the factors that may be involved in producing this decreased resistance to infection is the decreased production of antibodies. Williams et al.[430] reported that lead binds antibodies *in vitro* and could potentially do so *in vivo*. Chronic exposure to mice of lead acetate in drinking water produced a significant decrease in antibody synthesis, particularly gamma globulins.[431]

Phagocytosis (ingestion of foreign material by a cell specialized for that purpose) by alveolar macrophages is believed to be an important step in the removal of dust particles and bacteria from the respiratory tract. Consequently, the activities of alveolar macrophages are important aspects of pulmonary defense. Bingham et al.[432] found that the continuous inhalation of lead sesquioxide aerosol (10 $\mu g/m^3$ to 150 $\mu g/m^3$) by rats for 3 to 12 months significantly reduced the number of alveolar macrophages. Electron microscopic examination of the lungs of rats that had inhaled particulate lead oxide (200 $\mu g/m^3$) for 14 days revealed ultrastructural damage (mitochondria and endoplasmic reticulum) to the alveolar macrophages and the type I alveolar epithelial cells. Biochemically, a considerable loss in the activity of the benzopyrene hydroxylating enzyme in the alveolar macrophages was observed by Bruch et al.[433]

Few studies have been made of the effects of lead on the immunologic system in man. Reigart and Graber[434] studied 12 preschool children having elevated free erythrocyte protoporphyrin and blood levels ≥ 40 μg/dl and seven nonlead-burdened children for evidence of impairment of their immunological responses. They found no differences between the control group and the lead-exposed group with reference to complement levels, to immunoglobulins, or to anamnestic response to the tetanus toxoid antigen.

Hicks[435] points out that there is a need for systematic epidemiological studies on the effects of elevated lead levels on the incidence of infectious diseases in man. The paucity of information cannot support the formulation of any dose-response relationship at this time.

11.12 THE GASTROINTESTINAL SYSTEM

Colic is usually a consistent early symptom of lead poisoning, warning of much more serious effects that are likely to occur with continued and prolonged lead exposure. Although most commonly seen in industrial exposure cases, colic is also a lead poisoning symptom present in infants and young children.

Beritic[436] reported on the cases of 13 of 64 men exposed on their jobs to occupational levels of lead. The 13 had colic, probably lead related, and constipation. They had blood lead levels ranging from a little less than 40 to 80 μg/dl as determined by polarography, a technique which tends to yield values lower than the actual blood levels. The diagnosis of lead-caused colic was supported by findings of high urinary coproporphyrin, excessive basophilic stippling, reticulocytosis, and some degree of anemia, all of which are other clinical signs of lead poisoning.

Although these symptoms are well documented in the literature, there are insufficient data by which to establish a dose-response relationship for an effect of lead on the gastrointestinal system.

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12. ASSESSMENT OF LEAD EXPOSURES AND ABSORPTION IN HUMAN POPULATIONS

12.1 INTRODUCTION

Although epidemiological studies provide the most directly relevant data for setting ambient air quality standards, such investigations are subject to methodological and practical difficulties. Of most interest are studies relating ambient air lead exposures directly to human health effects in various population groups. Unfortunately, few such studies exist. Standards setting, then, must rely on constructing (1) the linkage between exposures to environmental sources of lead and the incorporation of lead from those sources in various segments of the population as measured by blood lead levels and (2) the relationship between levels of lead in the blood and associated health effects.

This chapter will examine the details of studying blood lead levels in human populations. Included will be an examination of the statistical considerations of such investigations as well as a discussion of the characteristics of the frequency distribution of blood lead values and of how these may be used as tools in setting environmental standards. In addition, the effects of geographic and demographic variables on lead burdens will be considered. Finally, the epidemiological and clinical studies on the relationships between environmental lead exposures and human absorption will be described, and, where available, quantitative estimates of those relationships will be presented.

12.2 LEAD IN HUMAN POPULATIONS

In this section, the statistical approaches for assessing blood lead levels in human populations will be discussed, as will their applications and implications. This discussion will be followed by a description of findings relating to the geographic and demographic distributions of blood lead levels.

12.2.1 Statistical Descriptions and Implications

Many surveys have described blood lead values in human populations. Not unexpectedly, the investigators' choices of statistics to describe central tendencies and dispersion patterns are not uniform. This lack of uniformity makes comparison of the various studies quite difficult. For example, central tendencies are expressed as either arithmetic or geometric means, and the measures of dispersion also vary. Often the arithmetic mean of the distribution is much larger than the geometric mean.

12.2.1.1 FORM OF THE DISTRIBUTION OF BLOOD LEAD LEVELS

Several authors have either suggested or implied that the distribution of blood lead levels for any relatively homogeneous population closely follows a lognormal distribution.[1-3] Lognormality has also been noted for other metals, such as ^{90}Sr in bones of human populations.[4] Snee has suggested that the Pearson system of curves provides a slightly better fit for the data of Azar et al. than the lognormal,[5] but the improvement derived from this system does not seem sufficient to warrant the use of this little-known technique. Yankel et al.[1] and Tepper and Levin[2] both found their lead data to be lognormally distributed. Further analysis of the Houston study of Johnson et al.,[6] the Southern California study of Johnson et al.,[7] and the study of Azar et al.[3] also confirmed that a lognormal distribution provided a good fit to the data. For these reasons, much of what is presented in this chapter is based on the acceptance that homogeneous populations have a lognormal distribution of blood lead values.

The lognormal distribution and its application to biological measurements are discussed by several authors.[4,8,9] A variable is said to have a lognormal distribution if the logarithm of the variable is normally distributed. Because of the skewed nature of the lognormal distribution, the median (50th percentile) is a more meaningful estimate of central tendency than the arithmetic mean. For the normal distribution, the best estimate of the median is $\bar{X}$, the simple arithmetic mean. For the lognormal distribution, the best estimate of the median is the geometric mean (GM):

$$GM = \mathrm{Exp}[\sum_{i=1}^{n} (\ln(X_i))/n]. \quad (12\text{-}1)$$

The standard deviation of the logarithms is:

$$S = [\sum_{i=1}^{n} (\ln(X_i) - \ln(GM))^2/n-1]^{1/2}. \quad (12\text{-}2)$$

The geometric standard deviation, also known as the standard geometric deviation, is given by:

$$GSD = \mathrm{Exp}(S).$$

If only the arithmetic mean, $\bar{X}$, and arithmetic standard deviation, SD, are given, then the geometric mean and the geometric standard deviation can be estimated by:[10]

$$\hat{GM} = \bar{X}/(1 + SD^2/\bar{X}^2)^{1/2} \quad (12\text{-}3)$$

and

$$\hat{GSD} = \mathrm{Exp}[(\ln(SD^2/\bar{X}^2 + 1))^{1/2}]. \quad (12\text{-}4)$$

The geometric standard deviation must be interpreted differently than the arithmetic standard deviation. Using the SD, approximately 68 percent of the population will fall between (mean - SD) and (mean + SD). These same limits for the lognormal distribution become GM/GSD and (GM)(GSD). For example, if a population has a geometric mean blood lead level of 20 with a GSD of 1.3, then 95 percent of the population will have blood lead levels between $20/(1.3)^{1.96}$ and $(20)(1.3)^{1.96}$ or 11.96 and 33.45.

12.2.1.2 PERCENTILE ESTIMATES OF THE LOGNORMAL DISTRIBUTION

From the GM and GSD, estimates of percentiles of the lognormal distribution can easily be obtained either numerically or graphically. Numerically, the pth percentile, X_p, is estimated by

$$\hat{X}_p = (\hat{GM})(\hat{GSD})^{z_p} \quad (12\text{-}5)$$

where z_p is the z value from a standard normal table. The following values are often used:

Percent	z_p	Percent	z_p	Percent	z_p
1	-2.326	25	-.674	95	1.645
2.5	-1.960	50	0.000	97.5	1.960
5	-1.645	75	0.674	99	2.326
10	-1.282	90	1.282	99.9	3.090

Another method of obtaining percentile estimates is a graphical one using lognormal probability paper. One point is placed where the geometric mean intersects the 50th percentile. A second point is placed where $(\hat{GM})(\hat{GSD})^{2.326}$ intersects the 99th percentile. A line drawn through these two points gives the estimated cumulative frequency distribution. Figure 12-1, for example, is drawn with an assumed geometric standard deviation of 1.3.

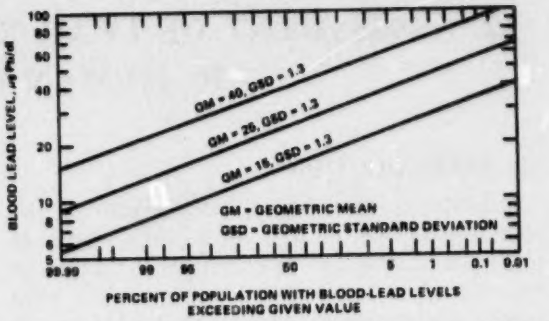

Figure 12-1. Estimated cumulative distribution of blood lead levels for populations in which the geometric mean level is 15, 25, or 40 μg/dl.

From this description of the distribution, estimates can be obtained of the percentage of blood lead values expected to exceed any given level for any given geometric mean blood lead level. For example, (Figure 12-1) in the populations with geometric mean blood lead levels of 15, 25, and 40 μg/dl whole blood, 0.1, 10, and 68 percent, respectively, will have blood levels exceeding 35 μg/dl.

As stated above, Figure 12-1 was drawn with a GSD of 1.3. The effect of varying the geometric standard deviations on the percentage exceeding a specified blood lead value is shown in Figure 12-2 because the value of the GSD has been shown to vary across studies (Table 12-1). A marked effect can be noted. It is very important, therefore, to be sure of

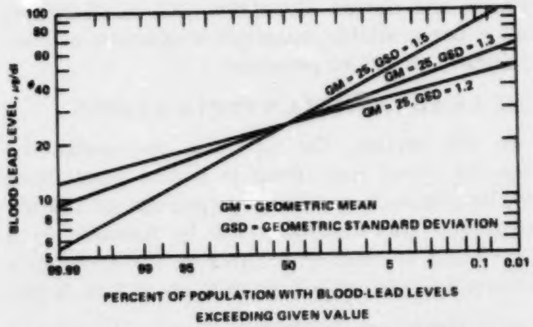

Figure 12-2. Estimated cumulative distribution of blood lead levels for populations having a geometric mean blood lead level of 25 μg/dl, but geometric standard deviations of 1.2, 1.3, or 1.5.

the value used for the geometric standard deviation if the lognormal distribution is to be used in setting environmental standards.

Because most blood lead data have been reported as arithmetic means and standard deviations, and because the raw data are not generally available, this chapter will use the term "mean" for arithmetic mean. The arithmetic standard deviations, when available, will be identified. If the geometric means are available, they will be reported as geometric means with the geometric standard deviation provided.

TABLE 12-1. ANALYSIS OF VARIANCE FOR THE LOGARITHMS OF BLOOD LEAD VALUES FOR SELECTED STUDIES (Geometric standard deviations given in parentheses)

Study	Population size	Replicates per observation	Number of duplicates	Population variance[a]	Within group variance[a]	Measurement variance
Idaho[1]	879	3	16[b]	0.190 (1.55)	0.072 (1.31)	0.012[b] (1.12)
Seven City Study[2]	1906	1	171	0.090 (1.35)	0.082 (1.33)	0.063 (1.28)
Southern California-Males[7]	64	2	64	0.224 (1.60)	0.181 (1.53)	0.216 (1.59)
Southern California-Females[7]	107	2	107	0.183 (1.53)	0.167 (1.51)	0.141 (1.45)
Houston[6]	189	2	189	0.182 (1.53)	0.069 (1.30)	0.094 (1.36)
Azar[3]	149	2-8	NA[c]	0.148 (1.47)	0.099 (1.37)	0.049 (1.25)

[a] Includes measurement variation.

[b] Based on a separate Center for Disease Control versus Idaho comparison of 16 samples of 1975 data, which are different from the 1974 data for the Idaho study.[1] The estimates of population and within group variance come from the original study.

[c] Not available.

12.2.1.3 VARIATION IN BLOOD LEAD VALUES

The total variation in blood lead values for any study is composed of three variance components: (1) between group, (2) within group or individual, and (3) method variation. The method variance results from both sampling and analytical measurement variations. The within group variance results from the difference in biological response among individuals with the same exposure as well as demographic differences in age, sex, race, socioeconomic status, and environmental background of the individuals in a group. The within group variance is a measure of the homogeneity of people in a group, but also includes method variance. The between group variance results from the differences in the composition of people in a group, such as police officers or housewives. In studying the effect of lead exposure on blood lead levels, it is necessary to separate these sources of variation to know whether the study results are meaningful. If the blood lead sampling and analysis errors are large, any effects of different lead exposure may not be seen. In a similar manner, if the group chosen for a study is not homogeneous, the within group variance may be so large that the differences in blood lead values cannot be interpreted as resulting from exposure. The sources of variation are estimated in Table 12-1 for several studies for which the raw data were available. The variation is expressed in terms of the natural logarithms of the blood lead values, and the calculations were made using standard analysis of variance techniques. The variances are converted to geometric standard deviations and these values are shown in parentheses.

Table 12-1 shows that a large portion of the total variation is caused by measurement variation, except possibly for the Idaho[1] study. The measurement variation was unusually large for the Southern California study,[7] suggesting that results from this study should be viewed with caution. Except for the Southern California study, the GSD for within group variation was consistently near 1.3. This number includes both biologic and measurement variation. It is possible for the measurement variation to exceed the within group variation if there is more than one reading per individual, however, as was the case in both the Southern California and Houston studies.

12.2.1.4 PROBLEM OF FALSE EXCEEDENCES

Lucas[11] has described a problem that he terms "false exceedences." For example, a lognormal distribution with a geometric mean of 25 and a geometric standard deviation of 1.3 will have 3.7 percent of the distribution above 40. As a hypothetical example, if half of the variation is caused by measurement variation, then the "true" distribution would have a geometric standard deviation of 1.2 and would have only 0.6 percent of the distribution above 40.

False exceedences become a real problem if a threshold value, such as 40, is determined from sources of data lacking a large measurement variation. In such cases, the estimated percentage of the distribution above a fixed level will be an overestimate as shown in the previous paragraph. It is extremely difficult to obtain more accurate estimates because the appropriate variance can only be estimated indirectly and only in cases where there are replicate measurements on the same individual. If, however, the threshold itself is estimated from data having this same measurement variation, then the problem is more difficult. In such cases, the observed variances including measurement variation may be more appropriate. As the technology of measurement improves, the problem will become much less significant.

12.2.2 **Geographic Variability in Human Blood Lead Levels**

Numerous studies have been conducted throughout the world establishing mean blood lead concentrations for various remote, rural, suburban, and urban populations. By examining the differences among the observed levels across these populations, inferences can be drawn concerning the ubiquity of lead exposures as well as their relative magnitudes. A word of caution, however, must be inserted here. Many of these data have been collected over a period of time in which measurement technology for blood lead determinations has changed and improved. Also, sometimes neither the methods of analysis nor the sampling scheme used have been reported.

Studies of remote populations have been used to estimate the natural background blood lead level for humans.[12-15] Likewise, studies comparing either rural or suburban populations have been used to establish the effect of urban living on blood lead levels. All these studies, however, can be used to demonstrate the broad variety of populations in which lead from all environmental sources has been found in people.

Only a few studies[12-15] have focused on remote populations. Goldwater and Hoover[12] conducted an international study of urban and rural populations in which investigators from 14 countries participated; only non-occupationally exposed adults were studied. One laboratory did all the chemical analyses. Some of these populations — New Guinea aborigines, for example — were thought to be remote from the effects of industrialization. The mean and standard deviations of blood lead for the aborigines, however, were 22 and 5 μg/dl, respectively. Examination of their living habits could shed no light on the sources of this lead. In contrast to this, urban residents from Peru in the same study had a mean of 7 μg/dl and a standard deviation of 5 μg/dl.

Stopps[13,14] reported data on remote populations. Table 12-2 presents the blood lead means as ranging from 23 to 12 μg/100 g.

In contrast to the findings of Goldwater and Hoover[12] and Stopps,[13,14] Hecker et al.[15] in a more recent study of Amazon River Basin Indians, using anodic stripping voltammetry, found a mean blood lead of 0.83 μg/dl with a standard deviation of 0.59 in 90 subjects. The urinary levels were not quite as low as the blood leads (mean, 7.9 μg/dl; SD, 5.7), but still are low in comparison with the values reported in Goldwater and Hoover.[12]

TABLE 12-2. BLOOD LEAD LEVELS OF REMOTE POPULATIONS[13,14]

Populations	Sample size	Blood lead, μg/100 g
Brazilian Indians	11	23
Marshall Islanders	33	23
Peruvian Indians	39	18
Islanders off Australia	28	17.5
Bushmen	68	16
New Guinea natives	67	13
East Africans	63	12

A number of studies have specifically contrasted blood lead results between rural, suburban, and urban populations.[2,16-21] Two of the methodologically better studies are those of Tepper and Levin,[2] and Nordman.[16] Tepper and Levin[2] conducted a study of the blood lead levels of 11 groups of housewives from 8 U.S. metropolitan areas. Three of these, Chicago, New York, and Philadelphia, had urbansuburan comparison groups. Table 12-3 displays the results of the contrasts between those groups as calculated by Hasselblad and Nelson.[22] In every case, a significant difference was obtained.

TABLE 12-3. AGE AND SMOKING-ADJUSTED GEOMETRIC MEAN BLOOD LEADS IN URBAN VERSUS SUBURBAN AREAS OF THREE CITIES

City	Blood Lead, μg %			
	Urban	Suburban	Urban excess	Significant
Chicago, IL	17.55	14.02	3.53	>0.01
Philadelphia, PA	20.12	17.88	2.24	>0.01
New York, NY	16.47	15.24	1.23	>0.01
Three cities together	18.05	15.71	2.34	>0.01

Nordman[16] studied a series of populations in Finland including downtown urban, suburban, and rural populations. No statistically significant differences were observed between urban and rural or suburban residents. But, interestingly, none of the populations studied, which included traffic policemen, streetsweepers, downtown Helsinki residents, and rural controls, had a mean blood lead level that exceeded 13.5 μg/dl.

Other studies permitting urban rural comparisons include those of Hofreuter et al.,[17] Creason et al.,[18] Scanlon,[19] Gershanik et al.,[20] and Cohen et al.[21] Hofreuter et al.,[17] in 1960, collected blood samples from about 120 people in each of 6 cities and from 162 people in a rural area (central Ohio). Table 12-4 displays the results of these comparisons. In all urban survey sites, the mean blood lead level was significantly higher than in the rural survey sites.

TABLE 12-4. BLOOD LEAD CONCENTRATIONS IN SIX URBAN AND ONE RURAL POPULATION

Survey site	No. of samples	Mean blood lead, μg/100 g	Urban excess
New Orleans, LA	130	22	8
Chicago, IL	97	20	6
New York, NY	112	20	6
Cincinnati, OH	137	20	6
Dallas, TX	128	18	4
Denver, CO	131	19	5
Rural	162	14	

Creason et al.[18] studied military recruits in the Chicago area at the time of their induction. By the very nature of the sample, only young male adults were included. Further, analysis was restricted to those having lived at the same home address for two or more years. The population was broken down by race and three residential locations, namely urban, suburban, and outstate. Median blood levels for whites were 22, 20, and 36 μg/dl for the urban, suburban, and outstate populations, respectively.

Scanlon[19] reported on umbilical cord blood lead levels for infants born to Boston area women. Mean blood lead levels for urban infants were 22.1 μg/dl compared with 18.3 μg/dl for the suburban newborn. This difference was not statistically significant.

Gershanik et al.[20] studying a larger sample of cord bloods in Shreveport, Louisiana, however, found a statistically significant difference between urban and suburban infant cord blood lead levels, 9.7 ± 3.9 versus 8.3 ± 2.4 μg/dl, respectively.

Cohen et al.[21] reported on a rural-urban comparison for children, aged 1 to 5 years, living in 2 rural counties and in Hartford, Connecticut. Although the 2 samples were adequately matched on age, there was a major racial/ethnic difference — the urban population being either black or Puerto Rican and the rural primarily white. The mean and standard deviation of the blood lead concentrations were 32.7 ± 14.8 and 22.8 ± 11.0 for the urban and rural populations, respectively.

Some of these same studies, as well as others, can be used to discern a wider picture of the variability of blood lead levels.[12-14,17] In the Goldwater and Hoover study,[12] urban population mean blood lead levels were found to range from 7 to 25 μg/dl, whereas the mean for rural areas ranged from 9 to 32 μg/dl. The wide range of means in both population types suggests that lead can be found in many locations.

Nordman[16] reviewed the available literature on blood lead levels and concluded that "the Pb-B mean values for occupationally unexposed rural and urban populations range from 10 to 26 μg/dl." Exceptions to this general range are found, however. Lower-than-usual blood lead levels have been reported from some parts of Sweden and Finland. There, levels in women were found to be 10 μg/dl.[16,23] On the other hand, higher-than-usual blood lead values have been reported from sections of Italy and France.[24-27] Zurlo et al.,[24] in particular, reported very high blood lead levels for adults in the Milan area, urban mean of 30 μg/dl for males and 23.7 μg/dl for females.

Data obtained from adults within the United States follow a similar pattern.[2,17,28] In data from Tepper and Levin,[2] differences were noted in the geometric mean blood lead among the 11 populations of housewives studied. The lowest blood lead values were found in Houston, Texas, with a GM and a GSD of 12.5 and 1.31, respectively, whereas the highest were found in Rittenhouse, a section of

Philadelphia — GM and GSD of 20.6 and 1.33, respectively.

In the 1960 Hofreuter et al. study,[17] blood samples were collected from people in six metropolitan areas and one rural control site. The mean blood lead values varied from 14 to 22 μg/100 g. The maximum observed values ranged from 38 to 60 μg/100 g.

Kubota et al.[28] studied blood lead levels in male residents of 19 intermediate-sized cities across the United States. Mean blood levels were found to vary from 7.25 μg/dl in Lafayette, Louisiana, to 20.34 μg/dl in Jacksonville, Florida. The highest reported value, 109.27 μg/dl, occurred in Fargo, North Dakota. A wide range in values was reported for each city, the largest being 5.91 to 109.27 μg/dl in Fargo. Further, the authors report three cities with mean blood lead levels below 8.00 μg/dl, namely Lubbock, Texas, 7.95; Geneva, New York, 7.65; and Lafayette, Louisiana, 7.25 μg/dl. These low values approximate those found in parts of Scandinavia.[16]

Workers at 23 DuPont Company plants were studied over a 5-year period, 1967 through 1971.[29] No time trend was noted for blood lead levels, and the samples were pooled per plant for the 5 years. The geometric mean values varied from a low of 15.5 μg/100 g for the Ashland, Wisconsin, plant to a high of 21.6 μg/100 g at the Los Angeles, California, plant. The overall geometric mean for the 23 locations was 18.2 μg/100 g.

Data addressing geographic variation of blood lead values in children are not as extensive. For the United States, Fine et al.,[30] Baker et al.,[31] and Joselow et al.[32] provided the best available information. Fine et al.[30] studied 6151 children aged 1 to 6 years in 14 intermediate-sized cities in Illinois in 1971. Blood lead values (Table 12-5) were determined by an atomic absorption technique. Mean values for cities ranged from 19.8 to 32.9 μg/dl; the mean for all 14 cities was 25.5 μg/dl. These values are indicative of sources of lead in the children's environment.

TABLE 12-5. MEAN BLOOD LEAD VALUES FOR CHILDREN IN 14 INTERMEDIATE-SIZED CITIES IN ILLINOIS, 1971[30]

City	No. of children screened	% of city's children ages 1-6 yr screened	Mean blood lead value, μg/dl
Aurora	449	5.09	28.2
Springfield	670	7.28	31.5
Peoria	387	2.97	32.9
East St. Louis	376	4.09	28.6
Decatur	793	5.84	21.5
Joliet	383	4.54	27.8
Rock Island	285	5.60	25.0
East Moline	298	12.32	23.5
Harvey and Phoenix	226	4.90	22.6
East Chicago Heights	172	17.13	27.3
Chicago Heights	537	10.36	25.2
Robbins	103	6.78	22.2
Carbondale	264	17.46	28.5
Rockford	1,208	7.31	19.8
Total	6,151	6.14	25.5

Baker et al.[31] determined blood lead values for 1672 children aged 1 to 5 living in 19 towns containing smelters and 3 control towns. The smelter communities were selected for study because they had not previously been subject to thorough investigation. Blood lead values were determined by an atomic absorption technique.

The mean blood lead levels for the lead and copper smelter towns did not differ from those control towns, as shown in Table 12-6. The children living in zinc smelter towns, however, showed significantly higher blood lead values than the other three groups. The lowest mean blood lead value, 9.15 μg/dl, was found in children for McGill, Nevada, whereas the highest mean value was found for Bartlesville, Oklahoma, with 28.60 μg/dl.

Joselow et al.[32] compared the blood lead levels of children aged 3 to 5 years in Newark, New Jersey, and Honolulu, Hawaii, in 1973. The study included 152 children who were matched for age and sex into 2 groups of 76 from each city. The mean blood lead value for the Newark children was 28 μg/dl, considerably higher than that found in Honolulu children, 17 μg/dl.

12.2.3 Demographic Variables and Human Blood Lead Levels

Fewer data are available to evaluate the effects of age, sex, and race on blood lead levels.

Children consistently develop higher blood lead levels than do adults in the same environmental setting. In El Paso, Texas,[33] in 1972, 70 percent of children 1 to 4 years old living near a primary lead, copper, and zinc smelter had blood lead levels >40 μg/dl, and 14 percent exceeded 60 μg/dl. In children 5 to 9 years old, 45 percent exceeded 40 μg/dl, as did 31 percent of measurements in individuals 10 to 19 years old and 16 percent of those over 19.

In the vicinity of a primary lead smelter in Idaho in 1974, the geometric mean blood lead levels shown in Table 12-2 were obtained.[1] As can be seen from Table 12-7, children under 10 years of age consistently had higher blood lead values than older children and adults within the same environment.

TABLE 12-6. BLOOD LEAD LEVELS (WHOLE BLOOD) IN CHILDREN IN U.S. SMELTER AND COMPARISON TOWNS, 1975[31]

City	No. of samples	Mean	SE[a]	GM	GSD	Percent exceeding 35 μg/dl
Comparison towns						
Albuquerque, NM	81	17.70	0.63	16.8	1.39	0.0
Perryville, MO	85	16.88	0.74	15.8	1.42	2.4
Safford, AZ	92	15.26	0.71	13.8	1.57	1.1
Total	258	16.56	0.41	15.4	1.57	1.2
Lead smelter towns						
Bixby, MO	48	13.76	0.96	12.4	1.66	0.0
Glover, MO	23	12.05	1.19	11.1	1.58	0.0
Herculaneum, MO	87	18.80	0.94	17.2	1.54	8.0
Total	158	16.34	0.66	14.6	1.64	4.4
Copper smelter towns						
Ajo, AZ	105	12.55	0.46	11.7	1.45	0.0
Anaconda, MT	64	13.38	0.95	11.6	1.77	1.6
Copper Hill, TN	86	16.63	0.74	15.4	1.47	1.2
Douglas, AZ	97	20.47	0.86	18.9	1.49	3.1
Hayden, AZ	100	21.24	0.85	19.9	1.42	5.0
Hurley, MN	42	14.33	1.23	12.8	1.60	4.8
McGill, NV	50	9.15	0.52	8.9	1.45	0.0
Miami, AZ	94	17.00	0.74	15.5	1.59	3.2
Morenci, AZ	100	13.87	0.56	12.9	1.47	0.0
San Manuel, AZ	101	18.01	0.55	17.2	1.37	1.0
White Pine, MI	70	18.62	0.74	17.8	1.34	2.9
Total	909	16.36	0.25	14.8	1.58	2.0
Zinc smelter towns						
Amarillo, TX	84	22.34	1.16	20.9	1.41	4.8
Bartlesville, OK	87	28.60	1.91	23.6	1.92	31.0
Corpus Christi, TX	12	19.02	1.42	18.4	1.32	0.0
Monaco, PA	62	14.84	0.82	13.7	1.49	1.6
Palmerton, PA	102	17.51	0.60	16.5	1.42	1.0
Total	347	21.04	0.66	18.6	1.63	9.5

[a] SE = standard error

TABLE 12-7. GEOMETRIC MEAN AND GEOMETRIC STANDARD DEVIATIONS (IN PARENTHESES) OF BLOOD LEAD LEVELS BY AGE AND STUDY SECTOR (μg/dl)

Study sector	Age, years		
	< 10	10-19	>20
I	66 (1.33)	39 (1.26)	38 (1.32)
II	47 (1.30)	33 (1.23)	33 (1.33)
III	34 (1.26)	28 (1.40)	30 (1.35)

Likewise, a study of traffic exposure in Dallas, Texas,[34] found mean blood lead concentrations of 12 to 18 μg/dl in children as contrasted with 9 to 14 μg/dl in adults, when exposure levels are controlled.

Simpson et al.[35] summarized the results of 27 neighborhood screening programs conducted throughout the United States in the spring and summer of 1971. They found that children less than 3 years of age had a lower rate of elevated blood lead than children older than 3 years. Of those under 3 years, 25.8 percent had values of ≥ 40.0 μg/dl, whereas 31.4 percent of those 3 years of age or older had values ≥40.0 μg/dl.

Elam et al.[36] studied pediatric patients in a Chicago outpatient service. The proportion of children (Table 12-8) with blood lead values ≥ 50 μg/dl varied with age; the proportion over 50 μg/dl peaked at 18 to 30 months of age.

TABLE 12-8. PROPORTION OF CHILDREN WITH BLOOD LEAD VALUES BETWEEN 50 AND 99 μg/dl, BY AGE, CHICAGO 1971-1975[36]

Age, months	% Blood lead 50 to 99 μg/dl
6-17	24
18-30	40
31-42	16
43-52	12
55-66	7

A study of Philadelphia ghetto children[37] conducted in 1972 through 1973 provides data relevant to the relationship between age and blood lead level. The study population consisted of 1559 black children aged 6 months to 18 years of age. Table 12-9 presents the blood lead levels by age. In both

G6PD normal and deficient children, the blood lead pattern of increase and decrease by advancing age pertains. The only increase, but a substantial one, is observed between children less than 1 year of age and those 1 to 3 years old. Blood lead levels decrease in all succeeding age groups.

TABLE 12-9. MEAN BLOOD LEAD (μg%) BY AGE, SEX, AND G6PD STATUS IN 1559 URBAN BLACK CHILDREN[37]

Age, years	Sex	Number	G6PD normal	Number	G6PD deficient
<1	Both	61	19.1 ± 9.5	9	18.3 ± 8.2
	Males	32	19.5 ± 9.0	6	18.8 ± 8.2
	Females	29	19.2 ± 9.2	3	17.3 ± 8.4
1-3	Both	289	29.1 ± 14.6	40	33.2 ± 15.5
	Males	133	30.5 ± 15.1	30	33.1 ± 15.5
	Females	156	28.8 ± 11.0	10	33.6 ± 13.5
4-8	Both	404	25.0 ± 12.6	55	25.7 ± 13.4
	Males	177	24.6 ± 13.2	38	25.2 ± 12.9
	Females	227	25.1 ± 11.1	17	26.1 ± 13.5
9-13	Both	394	21.3 ± 10.4	44	23.0 ± 12.5
	Males	189	20.4 ± 10.9	29	22.1 ± 11.8
	Females	205	21.7 ± 9.7	15	24.8 ± 13.9
14-18	Both	242	18.7 ± 9.7	21	19.1 ± 9.9
	Males	94	18.5 ± 10.1	13	18.9 ± 9.3
	Females	148	18.8 ± 8.9	8	19.5 ± 10.1

Billick et al,[38] analyzed data from New York City lead screening programs from 1970 through 1976. The data include age in months, sex, race, residence expressed as health district, screening information, and blood lead values expressed in decades. Only the first screening data for individual children were included based on the analysis of venous blood. Only the data (178,588 values) clearly identified as coming from the first screening of a given child were used. All blood lead determinations were done by the same laboratory. The data presented are preliminary and an exhaustive analysis has not been completed. Table 12-10 presents the geometric means for the children's blood lead levels by age and

TABLE 12-10. GEOMETRIC MEAN BLOOD LEVELS IN NEW YORK CITY LEAD SCREENING PROGRAM
(Calculated on the basis of the Billick et al.[38] data)

Group and year	Age, months						
	1-12	13-24	25-36	37-48	49-60	61-72	73+
Blacks							
1970	27.2	31.2	31.2	28.4	31.4	22.9	25.7
1971	25.2	29.7	30.4	29.8	28.7	27.7	27.0
1972	22.3	26.3	26.7	25.8	25.0	24.3	23.8
1973	22.6	26.9	26.3	25.6	24.5	24.1	23.1
1974	22.2	25.7	25.5	24.4	23.7	22.2	22.1
1975	20.5	22.9	22.9	22.3	21.7	21.8	19.6
1976	18.1	20.7	21.2	20.9	20.3	19.2	19.3
Hispanic							
1970	21.5	24.9	25.5	23.9	24.1	24.5	24.0
1971	19.9	22.9	25.0	24.9	24.4	23.9	23.9
1972	18.7	20.6	22.1	22.6	22.1	22.0	21.3
1973	20.1	21.8	22.5	23.1	22.2	21.6	21.7
1974	19.7	21.4	23.0	22.6	22.1	20.1	20.3
1975	17.4	19.6	20.6	20.9	20.6	20.0	18.5
1976	17.9	18.6	19.2	19.3	19.2	18.2	18.4
Whites							
1970	21.0	23.9	24.7	25.0	23.7	24.9	22.5
1971	19.9	22.8	22.9	23.0	23.9	21.9	21.7
1972	17.1	20.2	22.0	21.1	21.2	21.4	20.6
1973	20.3	21.5	21.9	22.1	20.6	21.6	21.1
1974	18.6	20.5	20.0	21.1	21.4	21.3	19.6
1975	19.1	20.0	19.0	18.2	19.8	18.0	17.3
1976	20.7	17.2	19.1	18.7	18.4	17.7	17.5

race for the 7 years. It should be mentioned that the means presented were derived by EPA from the raw data provided by Billick et al.[38] Because the blood lead levels were available to the nearest 10 μg/dl, the midpoints of each interval were used to calculate the geometric means. These means were calculated for each 2-month interval for each age and ethnic group and were then combined across the six 2-month intervals using an unweighted geometric mean so as to minimize any seasonal effects.

It should be noted that all racial/ethnic groups show an increase in geometric mean levels from < 1 to 1 to 2 years of age. Figure 12-3 shows the trends for 1970. Similar patterns hold for other years. The differences in age-associated patterns for the three racial/ethnic groups may be influenced by the substantial differences in population sizes for the groups: whites were the smallest group, Hispanics were next, and blacks the largest. Table 12-11 shows the size of the groups for the 7 years.

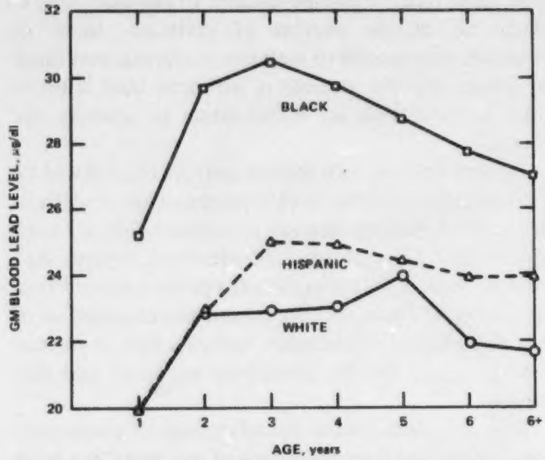

Figure 12-3. Geometric means for blood lead values by race and age, New York City, 1971.

TABLE 12-11. NUMBER OF CHILDREN'S INITIAL SCREENS IN NEW YORK CITY PROGRAMS BY RACE/ETHNICITY AND YEAR, 1970-1977[38]

Year	White	Black	Hispanic
1970	1,282	8,839	8,251
1971	2,796	23,174	18,740
1972	1,350	16,730	10,153
1973	823	9,722	6,875
1974	601	4,139	2,498
1975	656	4,585	2,620
1976	491	3,755	2,178

It is of interest to note that the age-associated pattern observed in the United States was not seen in a West German[39] study. In that study, 363 children of ages 8 days to 8 years showed increasing mean blood lead levels with age: 3.3 ± 2.6 μg/dl in the first year of life, increasing with each year to a mean of 11.5 ± 4.9 μg/dl at age 6 to 8.

In contrast to studies of children, most studies of adult populations do not show any marked effect of aging on blood lead levels.[17,40,41] Nordman found that males and females over the age of 65 years had lower blood lead values than the rest of the adult population in his study.[16]

Effects of sex on blood lead levels appear to be age dependent. Adult females are commonly found to have lower levels than males.[2,16,17,23,24] Among children, however, sex does not appear to be a differentiating factor.[42,43] Tepper and Levin[2] have suggested that the differences found in blood lead levels of adult men and women are not the result of either differences in lead intake from food or from differences in hematocrit levels between them.

Data for the assessment of race as a factor in blood lead levels are relatively scarce.[18,25,38,44,45] The earlier studies[18,44] report only the number of cases above a specified blood lead level. One study[18] shows higher lead levels for blacks than Puerto Ricans, but the other[44] reports that blacks had higher levels than nonblacks.

In their study of military recruits, Creason et al.[18] compared white and black subjects. Data in Table 12-12 show higher mean values for all black groups than for the whites.

TABLE 12-12. BLOOD LEAD LEVELS (μg/dl)[18] IN MILITARY RECRUITS, BY RACE AND PLACE

	Black			White		
Place	Number	Mean	90th percentile	Number	Mean	90th percentile
Urban	58	38	85	203	31	69
Suburban	4	80	124	218	27	54
Outstate	15	59	105	406	39	71

The Billick et al.[38] data show higher geometric mean blood lead values for blacks than for Hispanics or for whites. Table 12-13 presents these geometric means for the three racial/ethnic groups for 7 years. The consistency of the association is remarkable.

Numerous data have been published showing the effect of various occupations on blood lead levels.[16,25,40,46] In general, these data support the conclusion that workers exposed to automobile exhaust, lead fumes, or dust in manufacturing carry higher lead burdens than those who do not.

TABLE 12-13. GEOMETRIC MEAN BLOOD LEAD LEVELS (μg/dl) IN NEW YORK LEAD SCREENING PROGRAM, 1970-1976, FOR CHILDREN UP TO 72 MONTHS OF AGE, BY RACE AND YEAR[36]

Year	Black	Hispanic	White
1970	28.6	24.0	23.8
1971	28.5	23.4	22.4
1972	25.0	21.3	20.4
1973	25.0	21.9	21.3
1974	23.9	21.6	20.8
1975	22.0	19.8	19.0
1976	20.0	18.7	18.6

12.3 RELATIONSHIPS BETWEEN EXTERNAL EXPOSURES AND BLOOD LEAD LEVELS

In previous chapters, it has been shown that lead:

1. Is emitted from various sources, primarily automobiles and industrial operations.
2. Is distributed across the environment.
3. Is capable of being absorbed into the human body.

This section will describe the relationships observed between the different environmental exposures and the resulting absorption as measured by blood lead levels.

Lead that is emitted from mobile sources, e.g. automobile exhausts, and from stationary sources, e.g. industrial operations, either remains in the air or falls out, as discussed in Chapter 6. Studies have shown a buildup of lead in soil and dust as a result of emissions from these two sources. Further, the lead in soil and dust does not derive only from these sources but, in addition, from the deterioration and erosion of lead based paint. Therefore, although soil and dust are direct sources of human exposure to lead, they must also be viewed in terms of the primary mobile and stationary sources of the lead. Consequently, studies that examine only ambient air lead exposures may, in fact, underestimate the total contribution of airborne lead to the population's lead burden.

Efforts to estimate experimentally the relative importance of combustion of leaded gasoline to total lead burden in humans have only recently been initiated. Manton has presented evidence from a preliminary study using lead isotope ratios.[47] His findings suggest that automobiles supplied between 7 ± 3 and 41 ± 3 percent of the lead in blood of Dallas residents during 1972 to 1973. Garibaldi et al.,[48] in a major study being conducted in Italy, are attempting such allocations on a much larger scale. It is hoped that these data will be available shortly.

Because multiple sources of lead do exist and because each can contribute to the total lead burden of man, an important question to be addressed is the contribution of each source to the total body burden. In this section, individual studies examining the contribution from the major environmental sources of lead, that is, air, soil-dust, paint, food, and water, will be discussed.

12.3.1 Air Exposures

Studies of the relationship of air exposures to blood lead levels may be separated into two main categories: epidemiological and clinical.

Epidemiological studies in turn may be grouped into three types: those pertaining to populations exposed to mobile sources of emission, those of populations exposed to stationary sources, and those in which only the amount of airborne lead is taken into account with no effort made to identify the source.

Studies dealing with mobile sources of lead will be discussed first, followed by a presentation of stationary sources studies. Studies concerned with air lead levels regardless of sources will then follow, and clinical studies will complete the presentation. From this array, the studies that permit the calculation of the quantitative relationship between lead in air and lead in blood will be selectively analyzed and discussed.

Clinical studies have the advantage of permitting precise control over the levels of exposure but have the disadvantages of studying people under somewhat artifical conditions and of dealing, by necessity, with very few subjects. All clinical studies to be presented were limited to adults. Epidemiological studies have the advantage of studying people in their natural state, but frequently have the disadvantage of rather imprecise estimates of the exposures encountered. These studies allow estimates of the relationship to be made for both adults and children.

12.3.1.1 MOBILE SOURCE STUDIES

12.3.1.1.1 Studies in the United States. A 1973 Houston study examined the blood lead levels of parking garage attendants, traffic policemen, and adult females living near freeways.[6] A control group for each of the three exposed populations was selected by matching for age, education, and race. Unfortunately, the matching was not altogether successful; traffic policemen had less education than their controls and the garage employees were younger than their controls. Females were matched adequately, however. The findings for the six groups studied are presented in Table 12-14. It should be noted that the mean blood lead values for traffic policemen and parking garage attendants, two groups regularly exposed to higher concentrations of automotive exhausts, were significantly higher than the means for their relevant control groups. Statistically significant differences in mean values were not found, however, between women living near a freeway and control women living at greater distances from the freeway.

TABLE 12-14. MEAN BLOOD LEAD LEVELS FOR STUDY AND CONTROL GROUPS, HOUSTON[6]

Group	Mean, μg/dl	SD	Sample size	
Policemen	23.1	9.21	141	$P = 0.05$
Controls	18.4	7.38	150	
Garage attendants	28.3	10.33	119	$P = 0.05$
Controls	21.3	9.70	95	
Women living near freeway	12.9	4.47	120	$P > 0.05$
Controls	11.9	4.28	117	

A California study[7,49] examined blood lead levels in relation to exposure from automotive lead in two communities, Los Angeles and Lancaster (a city representative of the high desert). Los Angeles residents studied were individuals living in the vicinity of heavily traveled freeways within the city. They included males and females, aged 1 through 16, 17 through 34, and 35 and over. The persons selected from Lancaster represented similar age and sex distributions. On two consecutive days, blood, urine, and feces samples were collected. Air samples were collected from one Hi-Vol sampler in Los Angeles, located near a freeway, and two such samplers in Lancaster. The Los Angeles sampler collected for 7 days; the 2 in Lancaster were utilized for 14 days. On the first day of air sampling, soil samples were collected in each area in the vicinity of study subjects.

Lead in ambient air along the Los Angeles freeway averaged 6.3 ± 0.71 μg/m^3, and in the Lancaster area the average was 0.6 ± 0.21 μg/m^3. The mean soil lead in Los Angeles was 3633 μg/g, whereas that found in Lancaster was 66.9 μg/g. Higher concentrations of lead were found in the blood of children, as well as younger and older adults living near the freeway, than in individuals living in the control area. Table 12-15 shows the mean blood lead values for the six groups. Differences between Los Angeles and Lancaster groups were significant with the sole exception of the older males.

TABLE 12-15. ARITHMETIC AND GEOMETRIC MEAN BLOOD LEAD LEVELS (μg/dl) FOR LOS ANGELES AND LANCASTER, CA, BY SEX AND AGE[7]

	Los Angeles				Lancaster				
Groups by sex and age, years	N	Mean	SE[a]	Geometric mean	N	Mean	SE	Geometric mean	Significance of difference p[b]
Total	126	16.4	0.7	14.6	119	10.5	0.4	9.6	<<.001
Males	56	19.3	1.1	17.2	50	11.8	0.6	10.8	<<.001
1-16	20	23.5	2.5	20.8	21	11.1	0.8	10.4	<<.001
17-34	29	16.6	1.1	15.1	18	11.8	0.9	10.9	.003
35-	7	18.5	2.0	17.1	11	13.0	2.0	11.1	.09
Females	70	14.2	0.7	12.8	69	9.6	0.4	8.8	<<.001
1-16	18	16.7	1.8	14.9	25	10.2	0.7	9.6	<.001
17-34	41	12.9	0.6	11.8	16	9.1	1.2	8.0	<.001
35-	11	14.7	1.5	13.4	28	9.3	0.5	8.7	<.001

[a] Standard error.
[b] t test.

It has been pointed out by Snee that, in the high-traffic-density area, the reported 29 percent of samples in children 1 through 16 years old exceeding 40 μg/dl represented 5 individuals.[50] For 3 of these a second blood sample showed approximately 20 μg/dl; a second sample was not collected from the other 2. The disparity between blood samples taken on consecutive days from children in the study calls into question the validity of using these values to quantify the air lead to blood lead relationship. The differences between samples for adults, although somewhat larger than those found in other studies, appear acceptable for use in calculations, however.

A study of the effects of lower-level urban traffic densities on blood lead levels was undertaken in Dallas, Tex., in 1976.[34] The study consisted of two phases. One phase measured air-lead values for selected traffic densities and conditions, ranging from ≤1,000 to about 37,000 cars/day. The second phase consisted of an epidemiological study of traffic density and blood lead levels among residents. Figure 12-4 shows the relationship between arithmetic means of air lead and traffic density. As can be seen from the graph, a reasonable fit is shown.

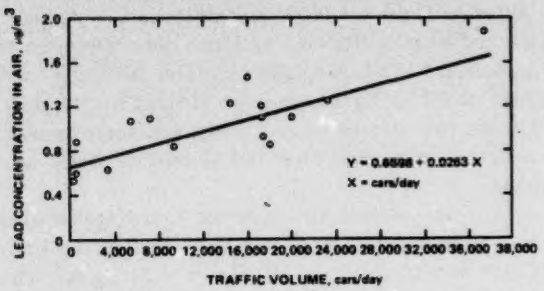

Figure 12-4. Arithmetic mean of air lead levels by traffic count, Dallas, 1976.[34]

In addition, during this phase, data for indoor-outdoor comparisons of air lead levels were collected. In two areas, with traffic densities of 10,000 and 20,000 cars/day, high volume samplers measured air lead outside of selected houses. At the same time, indoor air lead values for these houses were also collected. Table 12-16 shows the findings. Approximately a tenfold difference was found between indoor-outdoor values in both locations. It has been postulated that at least part of this difference is the result of using air conditioners.

TABLE 12-16. MEAN AIR LEAD LEVELS ($\mu g/m^3$) INDOORS AND OUTDOORS AT TWO TRAFFIC DENSITIES, DALLAS, TEX. 1976[34]

	10,000 cars/day		20,000 cars/day	
	Indoor	Outdoor	Indoor	Outdoor
Mean	0.182	0.918	0.199	2.105
N	9	9	5	5

In addition, for all distances measured (5 to 100 ft from the road), air lead concentrations declined rapidly with distance from the street. At 50 ft concentrations were about 55 percent of the street concentration; at 100 ft concentrations were less than 40 percent of the street concentrations. In air lead collections from 5 to 100 ft from the street, approximately 50 percent of the airborne lead was in the respirable range (< 1 μm) and the proportions in each size class remained approximately the same as the distance from the street increased.

Soil lead concentrations were higher in areas with greater traffic density (Table 12-17). The maximum soil level obtained was 730 μg/g.

TABLE 12-17. SOIL LEAD LEVELS BY TRAFFIC DENSITY[34]

Traffic density, vehicles/day	Soil lead levels, μg/g
<1,000	73.6
1,000-13,499	92.2
13,500-19,499	110.9
>19,500	105.9

Dustfall samples for 28 days from 9 locations showed no relationship to traffic densities, but outdoor levels were at least 10 times the indoor concentration in nearby residences.

In the second phase, three groups of subjects, 1 to 6 years old, 18 to 49 years old, and 50 years and older, were selected in each of 4 study areas. Traffic densities selected were: < 1,000, 8,000 to 14,000, 14,000 to 20,000, and 20,000 to 25,000 cars/day. The study groups averaged about 35 subjects, although the number varied from 21 to 50. The smallest groups were from the highest traffic density area. No relationship between traffic density and blood lead levels in any age groups was found (Figure 12-5). Blood lead levels were significantly higher in children, 12 to 18 μg/dl, than in adults, 9 to 14 μg/dl.

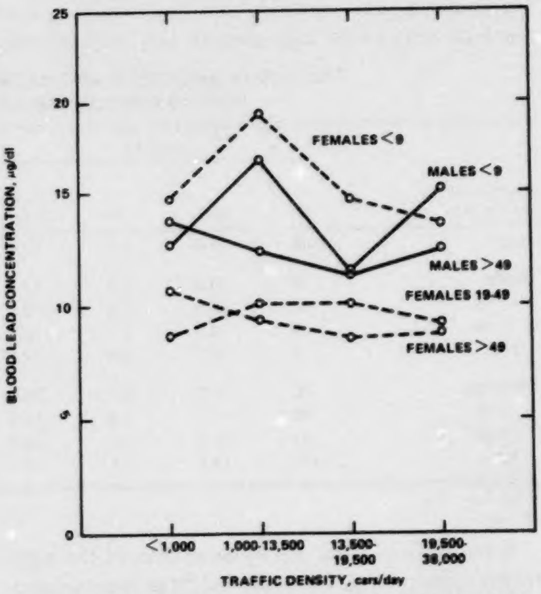

Figure 12-5. Blood lead concentration and traffic density by sex and age, Dallas, 1976.[34]

Galke et al.[43] studied blood lead levels in 187 South Carolina children 1 to 5 years old in relation to lead in soil and to automobile traffic. The arithmetic mean blood lead level was related to both factors, as shown in Table 12-18.

TABLE 12-18. BLOOD LEAD CONCENTRATIONS IN RELATION TO SOIL LEAD CONCENTRATIONS AND TRAFFIC DENSITY[43]
(µg/dl)

Soil lead concentrations, µg/g	Automobile traffic density		
	Low mean (951-1677 cars/day)	High mean (2446-9637 cars/day)	All densities
<585	32 (7)[a]	41 (8)	35 (8)
>585	36 (10)	43 (11)	41 (11)
Total	34 (9)	42 (10)	38 (10)

[a] Standard deviation of a single observation.

Caprio et al.[51] compared blood lead levels and proximity to major traffic arteries in a study, reported in 1971, that included 5226 children in Newark, New Jersey. Over 57 percent of the children living within 100 ft of roadways had blood lead levels greater than 40 µg/dl. For those living between 100 and 200 ft from the roadways, more than 27 percent had such levels; and at distances greater than 200 ft, 31 percent exceeded 40 µg/dl. Table 12-19 indicates that the effect of automobile traffic was seen only in the group that lived within 100 ft of the road.

TABLE 12-19. BLOOD LEAD LEVELS IN CHILDREN AGED 1 TO 5 IN NEWARK, NJ, IN RELATION TO DISTANCE OF RESIDENCE FROM A MAJOR ROADWAY, 1971[51]
(µg/dl)

Distance of residence from roadway, ft	Percent blood lead levels			Number
	<40	40-59	>60	
<100	42.6	49.3	8.1	758
100-200	72.4	24.2	3.4	507
>200	68.4	26.9	4.7	3961
number	3401	1562	263	5226

No other sources of lead were considered in this study. Data from other studies on mobile sources indicate, however, that it is unlikely that the blood lead levels observed in this study resulted entirely from automotive exhaust emissions.

Daines et al. studied black women living near a heavily traveled highway in New Jersey.[52] The subjects lived in houses on streets paralleling the highway at 3 distances, 3.7, 38.1, and 121.9 m. Air lead as well as levels for blood lead were measured. Mean annual air lead concentrations were 4.60, 2.41, and 2.24 µg/m^3, respectively, for the 3 distances. The mean air lead concentration for the area closest to the highway was significantly different from that in both the second and third, but the mean air lead concentration of the third area was not significantly different from that of the second. The results of the blood lead determinations paralleled those of the air lead. Mean blood lead levels of the 3 groups of women, in order of increasing distance, were 23.1, 17.4, and 17.6 µg/100 g, respectively. Again, the first group showed a significantly higher mean that the other two, but the second and third groups' blood lead levels were similar to each other. Daines et al.,[52] in the same publication, reported a second study in which the distances from the highway were 33.5 and 457 meters and where the subjects were white upper middle class women. Although the air lead levels were trivially different at these two distances, the blood lead levels did not differ. Because the residents nearest the road were already 33 m (+ 100 ft) from it and because other studies had shown an exponential decline in air lead levels with increasing distance from the road, reaching background air lead levels at 250 ft, the explanation may lie in the fact the air lead levels, although statistically different, were insufficient to be reflected in the blood lead levels. It is not possible to substantiate this possibility because the observed air lead values for the two distances were not reported.

In 1964, Thomas et al.[53] investigated blood lead levels in 50 adults who had lived for at least 3 years within 250 ft of a freeway (Los Angeles) and those of 50 others who had lived for a like period near the ocean or at least 1 mile from a freeway. Mean blood lead levels for those near the freeway were 22.7 ± 5.6 for men and 16.7 ± 7.0 µg/dl for women. These concentrations were higher than for control subjects living near the ocean: 16.0 ± 8.4 µg/dl for men and 9.9 ± 4.9 µg/dl for women. The higher values, however, were similar to those of other Los Angeles populations. Measured mean air concentrations of lead in Los Angeles for October 1964 were 12.25 ± 2.70 µg/m^3 at a location 30 ft from the San Bernardino freeway; 13.25 ± 1.90 µg/m^3 at another location 40 ft from the same freeway; 6.40 ± 2.15 µg/m^3 at a fourth floor location 300 ft from the freeway; and 4.60 ± 1.92 µg/m^3 1 mile from the nearest freeway. The investigators concluded that the differences observed were consistent with coastal-inland atmospheric and blood lead gradients in the Los Angeles basin and that the effect of residential proximity to a freeway (25 to 250 ft) was not demonstrated.

12.3.1.1.2 British studies. In a Birmingham, England, study, mean blood lead levels in 41 males and 58 females living within 800 m of a highway interchange were 14.41 and 10.93 µg/dl, respectively, just prior to the opening of the interchange in May 1972.[54] From October 1972 to February 1973 the respective values for the same individuals were 18.95 and 14.93 µg/dl. In October 1973 they were

23.73 and 19.21 $\mu g/dl$. The investigators noted difficulties in the blood collection method during the baseline period and changed from capillary to venous blood collection for the remaining two samples. To interpret the significance of the change in blood collection method, some individuals gave both capillary and venous blood at the second collection. The means for both capillary and venous bloods were calculated for the 18 males and 23 females who gave both types of blood.[55] The venous blood mean values for both these males and females were lower, 0.8 and 0.7 $\mu g/dl$, respectively. If these differences in means were applied to the means of the third series, the means for males would be reduced to 24.8 $\mu g/dl$ and that for the females to 18.7 $\mu g/dl$. These adjusted means still show an increase over the means obtained for the first series. On the other hand, discarding the means calculated for the first series and comparing only the means for venous bloods, namely series two and three, again shows an increase for both groups. The increase in blood lead values was larger than expected following the model of Knelson et al.[56] because air lead values near the road were approximately 1 $\mu g/m^3$. The investigators concluded that either the lead aerosol of very small particles behaved more like a gas so that considerably more than 37 percent of inhaled material was absorbed or that ingestion of lead-contaminated dust might be responsible.

Studies of taxicab drivers have employed different variables to represent the drivers' lead exposure,[57,58] one being night- versus day-shift drivers;[51] the other, mileage driven.[58] In neither case was any difference observed.

The studies reviewed show that automobiles produce sufficient emissions to increase air and nearby soil concentrations of lead as well as increase blood lead concentrations in children and adults. The problem is of greater importance when houses are located within 100 ft (30 m) of the roadway.

12.3.1.2 STATIONARY SOURCE STUDIES

12.3.1.2.1 Primary smelters. Most studies of nonindustry-employed populations living in the vicinity of industrial sources of lead pollution were triggered because evidence of severe health impairment had been found. Subsequently, extremely high exposures and high blood lead concentrations were found. The following studies document the health problems that can develop as well as some of the relationships between environmental exposure and human response.

12.3.1.2.1.1 *El Paso, Texas.* In 1972, the Center for Disease Control, formerly the Communicable Disease Center, studied the relationships between blood lead levels and environmental factors in the vicinity of a primary smelter emitting lead, copper, and zinc located in El Paso, Texas, that had been in operation since the late 1800's.[33,59] Estimated lead emissions from this smelter were 297 metric tons in 1969, 519 metric tons in 1970, and 317 metric tons in 1971.[33] These figures, however, include only stack emissions; the quantities in fugitive emissions via ventilation, windows, etc., are unknown. Daily high-volume samples collected on 86 days between February and June 1972 averaged 6.6 $\mu g/m^3$ of lead. Concentrations ranged from 0.49 to 75 $\mu g/m^3$. These air lead levels fell off rapidly with distance, reaching, as would be expected, background values approximately 5 km from the smelter. Levels were higher downwind, however. High concentrations of lead in soil and housedust were found, with the highest levels occurring near the smelter. The geometric means of 82 soil and 106 dust samples from the sector closest to the smelter were 1791 and 4022 $\mu g/g$, respectively. Geometric means of both soil and dust lead levels near the smelter were significantly higher than those in study sectors 2 or 3 km farther away.

Sixty-nine percent of children 1 to 4 years old living near the smelter had blood lead levels > 40 $\mu g/dl$, and 14 percent had blood lead levels that exceeded 60 $\mu g/dl$. Concentrations in older individuals were lower; nevertheless, 45 percent of the children 5 to 9 years old, 31 percent of the individuals 10 to 19 years old, and 16 percent of the individuals above 19 had blood lead levels all exceeding 40 $\mu g/dl$. The data presented preclude calculations of means and standard deviations.

Data for people aged 1 to 19 years living near the smelter showed a relationship between blood lead levels and concentrations of lead in soil and dust. For individuals with blood lead levels >40 $\mu g/dl$, the geometric mean concentration of lead in soil at their homes was 2587 $\mu g/g$, whereas for those with a blood lead concentration <40 $\mu g/dl$, home soils had a geometric mean of 1419 $\mu g/g$. For housedust, the respective geometric means were 6447 and 2067 $\mu g/g$.

Analysis found the effect of length of residence to be important only in the sector nearest the smelter. Forty-three percent of the 1- to 19-year-olds who had lived there 2 or more years had blood lead values ≥ 40 $\mu g/dl$, whereas only 18 percent of the 1- to 19-year-olds who had lived there less than 2 years had similar levels.

Additional sources of lead were also investigated. A relationship was found between blood lead concentrations and lead release from pottery, but the number of individuals involved was very small. No relationships were found between blood lead levels and hours spent out of doors each day, school attendance, or employment of a parent at the smelter. The reported prevalence of pica also was minimal.

It was concluded that the primary factor associated with elevated blood lead levels in the children was ingestion or inhalation of dust containing lead. Data on dietary intake of lead were not obtained because the climate and proximity to the smelter prevented any farming in the area. It was unlikely that the dietary lead intakes of the children from near the smelter and farther away were significantly different.

12.3.1.2.1.2 *Kellogg, Idaho*. In 1970, EPA carried out a study of a lead smelter in Kellogg, Idaho.[60,61] The study was part of a national effort to determine the effects of sulfur dioxide, total suspended particulate, and suspended sulfates, singly and in combination with other pollutants, on human health. It focused on mixtures of the sulfur compounds and metals. Although it was demonstrated that children had evidence of lead absorption, insufficient environmental data were reported to allow further quantitative analyses.

In 1974, following the hospitalization of two children with suspected acute lead poisoning, CDC joined the State of Idaho in a comprehensive study of children in the area.[1,62] The studies conducted in this area unfortunately used a bewildering array of designations in their reports, but all are related to the same industrial complex.

The source of exposure was a smelter whose records showed that emissions of lead into the atmosphere averaged 8.3 metric tons per month from 1955 to 1964, 11.7 metric tons from 1965 to September 1973, and 35.3 metric tons from October 1973 to September 1974.[62] In September 1973, a fire destroyed the main filtration facility for the smelter. The study was initiated in September 1974, after two children were hospitalized with symptoms of lead poisoning. At that time, blood lead levels ≥40 µg/dl were found in 385 (41.9 percent) of 919 children less than 10 years old who were examined. About 99 percent of the 172 children living within 1.6 km of the smelter had blood lead values ≥40 µg/dl. The mean blood concentration declined with distance from the point of emission (Table 12-20). Blood lead levels were consistently higher in children 1 to 4 years old than in those 5 to 9 years old. In addition, higher levels in children were associated with reported active ingestion of lead-containing material (pica), with lower socioeconomic status, and with parental employment at the smelter or at a lead mine. A significant negative relationship between blood lead level and hematocrit value was found. Seven of 41 children (17 percent) with blood lead levels ≥80 µg/dl were diagnosed by the investigators as being anemic on the basis of hematocrit less than 33 percent, whereas only 16 of 1006 children (1.6 percent) with blood lead levels < 80 µg/dl were so diagnosed.

TABLE 12-20. GEOMETRIC MEAN BLOOD LEAD LEVELS BY AREA COMPARED WITH ESTIMATED AIR LEAD LEVELS FOR 1- TO 9-YEAR-OLD CHILDREN LIVING NEAR IDAHO SMELTER (Geometric standard deviations, sample sizes, and distances from smelter are also given)[a]

Area	GM blood lead, µg/dl	GSD	Sample size	Estimated air lead, µg/m³	Distance from smelter, km
1	65.9	1.30	170	18.0	0- 1.6
2	47.7	1.32	192	14.0	1.6- 4.0
3	33.8	1.25	174	6.7	4.0-10.0
4	32.2	1.29	156	3.1	10.0-24.0
5	27.5	1.30	188	1.5	24.0-32.0
6	21.2	1.29	90	1.2	about 75

[a] EPA analysis of data from Yankel et al.[1]

Although no overt neurologic disease was observed in children with higher lead intake, differences were found in nerve conduction velocity. Details of this finding were discussed in a previous chapter.

Beginning in 1971, ambient concentrations of lead in the vicinity of the smelter were determined from particulate matter collected in high-volume air samplers. Data indicated that monthly average levels measured in 1974 (Figure 12-6) were three to four times the levels measured in 1971.[63] Individual exposures to lead were estimated by interpolation from these high-volume data, and a strong correlation was found between the estimates and the measured blood lead levels (r + 0.72).

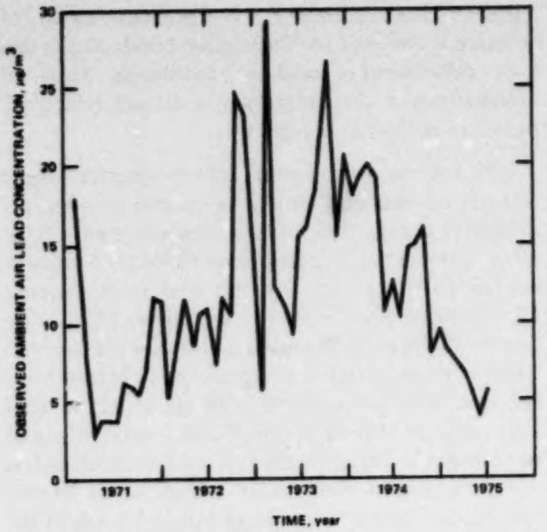

Figure 12-6. Monthly ambient air lead concentrations in Kellogg, Idaho, 1971 through 1975.[63]

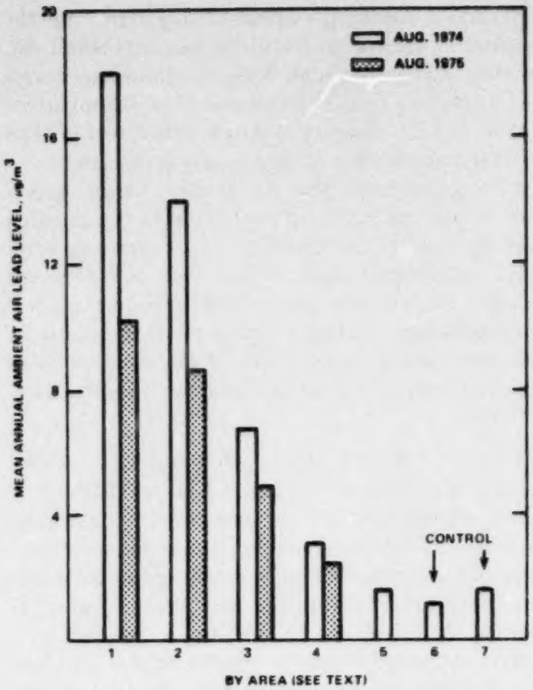

Figure 12-7. Annual ambient air lead concentration, by area, before the August 1974 and August 1975 surveys.[1]

Subsequently, Yankel et al. published additional information concerning the 1974 study as well as the results of a follow-up study conducted in 1975.[1] The follow-up was undertaken to determine the effectiveness of control measures initiated after the 1974 study.

Between August 1974 and August 1975, the mean annual air lead levels decreased at all stations monitored (Figure 12-7). In order of increasing distance from the smelter, the concentrations in the two years were 18.0 to 10.3 µg/m³, 14.0 to 8.5 µg/m³, 6.7 to 4.9 µg/m³, and, finally, 3.1 to 2.5 µg/m³ at 10 to 24 km. Similar reductions were noted in the housedust lead concentrations.

In a separate report, von Lindern and Yankel described reductions in blood lead levels of children for whom determinations were made in both years.[60] It was pointed out that the children with the highest blood lead levels in 1974 had been relocated; their removal and subsequent relocation would complicate any analysis in which they were included. To compensate for this, the authors also presented separately the blood lead levels for those children living in the same home both years. This greatly reduced the number of observations reported. The results (Table 12-21) demonstrate that significant reductions in blood lead concentration can be effected, and that they were observed in each study area. In areas III, IV, and V, all mean blood lead levels were <40 µg/dl.

The report of Yankel et al.[1] showed that there were reductions in environmental lead contamination between 1974 and 1975, and that the correlations between blood lead levels and environmental or demographic factors were consistent from one year to the next. Five factors influenced, in a statistically significant manner, the probability of a child developing an excessive blood lead level:

1. Concentrations of lead in ambient air (µg/m³).
2. Concentration of lead in soil (ppm).
3. Age (years).
4. Cleanliness of the home (subjective evaluation coded 0, 1, and 2, with 2 signifying dirtiest).
5. General classification of the parents' occupation (dimensionless).

Although the strongest correlation found was between blood lead level and air lead level, the authors concluded that it was unlikely that inhalation of contaminated air alone could explain the elevated blood lead levels observed.

Yankel and von Lindern reasoned that even though air lead was the principal source, a major route of exposure was the ingestion of lead in soil and dust.[1] They proposed that to protect the health

TABLE 12-21. MEAN BLOOD LEAD LEVELS IN CHILDREN LIVING IN VICINITY OF A PRIMARY LEAD SMELTER, 1974 and 1975

Group	Study area and data set									
	I		II		III		IV		V	
	N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$	N	$\bar{X}$
Blood levels >80 μg/dl[a] in 1974 test	—	90.2	—	80.0	—	—	—	—	—	—
Retested in 1975	7	52.3	1	61.0	—	—	—	—	—	—
Difference	—	-38.0	—	-19.0	—	—	—	—	—	—
Blood levels >60 but <80 μg/dl in 1974 test	—	64.5	—	69.6	—	—	—	—	—	61.0
Retested in 1975	18	47.4	8	50.3	—	—	—	—	3	51.0
Difference	—	-17.2	—	-19.3	—	—	—	—	—	-10.0
Blood levels <60 μg/dl in 1974 test	—	52.3	—	47.0	—	45.6	—	43.7	—	43.4
Retested in 1975	9	37.4	23	36.0	20	39.8	14	37.4	8	33.5
Difference	—	-14.9	—	-11.0	—	- 5.8	—	- 6.3	—	- 9.9

[a] Adapted from von Lindern and Yankel.[63]

of the children in this area the regulation of environmental standards must take into account all of these routes of exposure.

These investigators developed a mathematical model based on the 1974 data that included each of the five factors that had been shown to be correlated with increased blood lead levels. The model, shown below, can be used to estimate the effect of variations in the environmental factors on mean blood lead levels in children:

$$\ln(\text{Pb-B}) = 3.1 + 0.041\,(\text{Air}) + 2.1 \times 10^{-5}\,(\text{Soil}) + 0.087\,(\text{Dust}) + 0.018\,(\text{Age}) + 0.024\,(\text{Occupation}).$$

(See above for definition of units). (12-6)

12.3.1.2.1.3 *CDC-EPA study.* Baker et al.,[31] in 1975, surveyed 1774 children 1 to 5 years old, most of whom lived within 4 miles of 19 lead, copper, or zinc smelters located in various parts of the United States. Blood lead levels were modestly elevated near two of the 11 copper and two of the five zinc smelters. Although blood lead levels in children were not elevated in the vicinity of three lead smelters, their FEP levels were somewhat higher than those found in controls. Increased levels of lead and cadmium in hair samples were found near lead and zinc smelters; this was considered evidence of external exposure. No environmental determinations were made for this study.

12.3.1.2.1.4 *Meza Valley, Yugoslavia.* A Yugoslavian study in the Meza Valley investigated exposures to lead from a mine and a smelter over a period of years.[64-69] The mine and smelter are located near a river flowing in the valley. The smelter produces about 23,000 metric tons annually. After control equipment was installed on 1 of 2 lead-emitting stacks, emissions were calculated to be 203.2 metric tons/year. In 1967, 24-hr lead concentrations measured from 4 different days varied from 13 to 84 μg/m³ in the village nearest the smelter, and concentrations of up to 60 μg/m³ were found as far as 5 km from the source. Mean particle size in 1968 was <0.8 μm. The lead levels were about 25,000 ppm in the most contaminated area. Analysis of some common foodstuffs showed concentrations that were 10 to 100 times higher than corresponding foodstuff from the least exposed area (Mezica).[64]

After January 1969 when partial control of emissions was established at the smelter, weighted average weekly exposure was calculated to be 27 μg/m³ in the village near the smelter. In contrast to this, the city of Zagreb,[65] which has no large stationary source of lead, had an average weekly air lead level of 1.1 $\mu g/m^3$.

In 1968, the average concentration of ALA in urine samples from 912 inhabitants of six villages varied by village from 9.8 to 13 mg/liter. A control group had a mean ALA of 5.2 mg/liter. Data on lead in blood and the age and sex distribution of the villagers were not given.[64]

Of the 912 examined, 559 had an ALA level >10 mg/liter of urine. In 1969, a more extensive study of 286 individuals with ALA >10 mg/liter was undertaken.[66] ALA-U decreased significantly from the previous year. When the published data were examined closely, there appeared to be some discrepancies in interpretation. The exposure from dust and from food might have been affected by the control devices, but no data were collected to establish this. In one village, Zerjau, ALA-U dropped from 21.7 to 9.4 mg/liter in children 2 to 7 years of age. Corresponding ALA-U values for 8- to 15-year-olds and for adult men and women were reduced from 18.7 to 12.1, from 23.9 to 9.9, and from 18.5 to 9.0 mg/liter, respectively. Because lead concentrations in air[65] even after 1969 indicated an average exposure of 25 $\mu g/m^3$, it is possible that some other explanation should be sought. The author indicated in the report that the decrease in ALA-U showed "the dependence on meteorologic, topographic, and technologic factors."[66] Lead in blood was determined, but according to the report "determination of lead in blood could not be used for exposure evaluation because all obtained values were in the normal limits" (under 80 $\mu g/dl$ blood as defined by the author).[66] In light of current knowledge, this definition of normal levels is excessively high.

The excretion of nonchelated lead in urine in 8.5 percent of 209 individuals was above 0.1 mg/liter. The highest value recorded was 0.19 mg/liter. When treated with Ca EDTA, the mobilized lead in the urine of these individuals ranged from 0.5 to 4.2 mg/liter, indicating the presence of total body burdens ranging from normal to ten times normal.[66,68]

Another finding of this project was a significant increase in reticulocytes, especially in children.[66] Forty-seven percent of exposed adults complained of pain in their bones compared with only 3 percent of the controls.

Fugas et al.[69] in a later report estimated the time-weighted average exposure of several populations studied during the course of this project. Stationary samplers as well as personal monitors were used to estimate the exposure to airborne lead for various parts of the day. These values were then coupled with estimated proportions of time at which these exposures held. In Table 12-22, the estimated time-weighted blood lead values as well as the observed mean blood lead levels for these studied populations are presented. An increase in blood lead values occurs with increasing air lead exposure.

TABLE 12-22. MEAN BLOOD LEAD LEVELS IN SELECTED YUGOSLAVIAN POPULATIONS, BY ESTIMATED WEEKLY TIME-WEIGHTED AIR LEAD EXPOSURE[69]

Population	N	Time-weighted air lead $\mu g/m^3$	Mean blood lead level, $\mu g/dl$	SD
Rural I	49	0.079	7.9	4.4
Rural II	47	0.094	11.4	4.8
Rural III	45	0.146	10.5	4.0
Postmen	44	1.6	18.3	9.3
Customs officers	75	1.8	10.4	3.3
Street car drivers	43	2.1	24.3	10.5
Traffic policemen	27	3.0	12.2	5.1

12.3.1.2.1.5 *East Helena, Montana.* EPA in 1972 investigated a lead-emitting smelter complex in East Helena, Montana.[60] The quantities of lead emissions were not known. Air lead concentration, measured in 1969, yielded averages from several stations that varied from 0.4 to 4 $\mu g/m^3$; the maximum 24-hr value was found to be 15 $\mu g/m^3$. In the city of Helena, the average concentration was 0.1 $\mu g/m^3$. Lead in soil was found to be 4000, 600, and 100 $\mu g/g$ at distances of 1.6, 3.2, and 6.4 km (1, 2, and 4 miles), respectively, from the smelting complex. Uncontaminated soil near the Helena Valley showed a mean of 16 $\mu g/g$. Deposited lead (dustfall) was found to vary from 3 to 108 mg/m^2-month in East Helena and from 1 to 7 mg/m^2-month in Helena.

Studies on humans by Hammer et al.[61] were limited to children; lead values in hair and blood were found to be higher in East Helena than in Helena, the respective averages being 15.6 ± 5.1 and 11.6 ± 4.0 $\mu g/dl$ in blood and about 40 and 13 ppm in hair. The hair values indicated differential exposure to lead. However, in the opinion of the investigators, although the blood lead values indicated an elevated exposure, it had not been excessive. No adverse health effects had been noted in these children.

12.3.1.2.1.6 *Other smelter studies.* Other reports in the literature have also shown that people living near smelters have increased burdens of lead in their bodies.[70-72] It is clear, therefore, that emissions from primary lead smelters can cause elevated blood lead levels and other indicators of increased lead burdens in populations living near these stationary emission sources.

The question of the accuracy of the reported analytic results in these studies is difficult to address because they spanned a period of time in which major strides were taken in improving analytical technology. Hence, the more recent studies are likely, but not necessarily, to provide more accurate information.

Although many of the reports specified that the blood lead levels were done in duplicate, this unfortunately does not ensure their accuracy. This problem is discussed in more detail in Chapter 9.

12.3.1.2.2 Other industrial sources. Exposures from both a primary and secondary smelter in the inner-city area of Omaha, Neb. have been reported by Angle et al. in a series of publications.[73-76] Studied from 1970 to 1977 were children from an urban school immediately adjacent to a small battery plant and downwind from two other lead emission sources, schools in a mixed commercial-residential area, and schools in a suburban setting. Children's blood lead levels were obtained by macro technique for 1970 and 1971, but Delves micro assay was used from 1972 on. The difference for the change in techniques was taken into account in the presentation of the data. Air lead values were obtained by Hi-Vol samplers, and dustfall values also were collected. Table 12-23 presents the authors' summary of all the data, showing that as air lead values decrease and then increase, dustfall and blood lead values follow. The authors used regression models, both log-linear and semilog, to calculate air lead/blood lead ratios and obtained values of 10.04 and 0.4, respectively. The 0.4 value is equivalent to a ratio of 10.4 at an air lead level of 1.0 μg/m³.

TABLE 12-23. AIR, DUSTFALL, AND BLOOD LEAD CONCENTRATIONS IN OMAHA, NEB., STUDY, 1970-1977[a,75,76]

Group	Air, μg m³ (N)[b]	Dustfall, μg m³ - mo (N)[c]	Blood, μg dl (N)[d]
All urban children, site *m*:			
1970-71	1.48 ± 0.14(7;65)	—	31.4 ± 0.7(168)
1972-73	0.43 ± 0.08(8;72)	10.6 ± 0.3(6)	23.3 ± 0.3(211)
1974-75	0.10 ± 0.03(10;72)	6.0 ± 0.1(4)	20.4 ± 0.1(284)
1976-77	0.52 ± 0.07(12;47)	8.8 (7)	22.8 ± 0.7(38)
Children at school c, site *c*:			
1970-71	1.69 ± 0.11(7;67)	—	34.6 ± 1.5(21)
1972-73	0.63 ± 0.15(8;74)	25.9 ± 2.4(5)	21.9 ± 0.6(54)
1974-75	0.10 ± 0.03(10;70)	14.3 ± 4.1(4)	19.2 ± 0.9(17)
1976-77	0.60 ± 0.10(12;42)	33.9 (7)	22.8 ± 0.7(38)
All suburban children, site *r*:			
1970-71	0.79 ± 0.06(7;65)	—	—
1972-73	0.29 ± 0.04(8;73)	4.6 ± 1.1(6)	19.6 ± 0.5(81)
1974-75	0.12 ± 0.05(10:73)	2.9 ± 0.9(4)	14.4 ± 0.6(31)
1976-77	—	—	18.2 ± 0.3(185)

^{r}Pb-B • Pb-A = -0.95 (N = 10)
Pb-B = 10.04 Pb-A + 17.06

^{r}1n Pb-B • Pb-A = 0.91 (N = 10)
1n Pb-B = 0.4 Pb-A + 2.86

[a] Blood lead 1970-71 is by the macro technique, corrected for an established laboratory bias of 3 μg dl, macro-micro; all other values are by Delves micro assay.

[b] N = Number of months; number of 24-hour samples.

[c] N = Number of months.

[d] N = Number of blood samples.

Specific reports present various aspects of the work done. Black children in the two elementary schools closest to the battery plant had higher blood leads (34.1 μg/dl) than those in elementary and junior high schools farther away (26.3 μg/dl). Best estimates of the air exposures were 1.65 and 1.48 μg/m³, respectively.[73] The later study compared three populations: urban versus suburban high school students, ages 14 to 18; urban black children, ages 10 to 12, versus suburban whites, ages 10 to 12; blacks, ages 10 to 12, with blood lead over 20 μg percent versus schoolmates with blood lead levels below 20 μg percent.[74] The urban versus suburban high school children did not differ significantly, 22.3 ± 1.2 to 20.2 ± 7.0 μg/dl, respectively, with mean values of air lead concentrations of 0.43 and 0.29 μg/m³. For the 15 students who had environmental samples taken from their homes, correlation coefficients between blood lead levels and soil and housedust lead levels were 0.31 and 0.29 respectively.

Suburban 10-to-12-year-olds had lower blood lead levels than their urban counterparts, 17.1 ± 0.7 and 21.7 ± 0.5 μg/dl, respectively.[74] Air lead exposures were higher in the urban than in the suburban population, although the average exposure remained less than 1 $\mu g/m^3$. Dustfall lead measurements, however, were very much higher: 32.96 mg/m^2-month for urban 10-to-12-year-olds versus 3.02 mg/m^2-month for suburban ones.

Soil lead and housedust lead exposure levels were significantly higher for the urban black high-lead group than for the urban low-lead group. A significant correlation ($r = 0.49$) between blood lead and soil lead levels was found.

In a Dallas, Texas, study of two secondary lead smelters, the average blood lead levels of exposed children was found to be 30 μg/dl versus an average of 22 μg/dl in control children.[77] For the two study populations, the air and soil lead levels were 3.5 and 1.5 $\mu g/m^3$ and 727 and 255 ppm, respectively. Direct automobile traffic exposure was not considered.

In Toronto, Canada, the effects of two secondary lead smelters on the blood and hair lead levels of nearby residents have been extensively studied.[78,79] In a preliminary report, Roberts et al.[78] stated that blood and hair lead levels were higher in children living near the two smelters than in children living in an urban control area. Biologic and environmental lead levels were reported to decrease with increasing distance from the smelter stacks.

A later and more detailed report identified a high rate of lead fallout around the two secondary smelters.[79] Fallout in the vicinity of the smelters was caused primarily by large particulate fugitive emissions rather than stack emissions. Lead emissions from the two smelters were estimated to be 15,000 and 30,000 kg/yr. Lead concentrations in soil were as high as 40,000 and 16,000 ppm, respectively, close to the 2 smelters and dropped off exponentially with distance. They reached urban background levels of 100 to 500 ppm, 200 to 300 m from the smelter. Horn, in a later report, pointed out that the extremely high soil levels were the result of some samples containing scrap battery plate; in his report he states that the soil lead levels, excluding those contaminated samples, approached 8000 ppm in nonresidential areas and exceeded 4000 ppm in several residential yards.[80] He also pointed out several other deficiencies in the data.[80] A general criticism he leveled at the study's interpretation was that the authors concluded that soil lead was the main source of lead, a putative finding in Horn's view, especially considering that few soil samples were taken.

Lead concentrations in dustfall were much higher at 1 of the 2 smelters, exceeding 1500 mg/cm^2-month. These concentrations also exhibited an exponential decrease with distance similar to that observed for soils. Because the lead fallout occurred over a small area and consisted primarily of large particles (in some cases the mass median diameter was as large as 4.6 ± 1.3 μm), it was believed that the emissions originated mainly from dust-producing operations at low height rather than from stack emissions.[78]

Lead concentrations in air ranging from 1.0 to 5.3 $\mu g/m^3$ were only twice those found at other Toronto urban sites away from the smelter (0.8 to 2.4 $\mu g/m^3$). The range of daily concentrations was much greater. At 60 m from the stack, lead in 96 air samples ranged from 0.5 to 725 $\mu g/m^3$, whereas at 220 m 94 samples varied from <0.5 to 14 $\mu g/m^3$. Two groups of children living within 300 m of each of the smelters had geometric mean blood levels of 27 and 28 μg/dl, respectively; the geometric mean for 1231 controls was 17 μg/dl. Twenty-eight percent of the sample children tested near one smelter during the summer and 13 percent of the sample children tested near the second smelter during the winter had blood lead levels >40 μg/dl. Only 1 percent of the controls had blood lead levels >40 μg/dl. For children, blood lead concentrations increased with proximity to both smelters but this trend did not hold for adults generally.

Lead levels in hair samples averaged 41 μg/g in the smelter areas and 13 μg/g in the control area.[78] Blood lead and hair lead levels were found to be related, thus indicating a fairly constant rate of absorption. The authors concluded that for children with excessive lead absorption the major route of lead intake was ingestion of contaminated dirt and dust.[78,79] Increased excretion of δ-aminolevulinic acid and coproporphyrins was observed in most of these cases, and increased density of bone metaphyses was observed in four children.

Blood lead levels in 293 Finnish individuals aged 15 to 80 were significantly correlated with distance of habitation from a secondary lead smelter.[81] The geometric mean blood lead concentration for 121 males was 18.1 μg/dl; that for 172 females was 14.3 μg/dl. In 59 subjects who spent their entire day at home, a positive correlation was found between

m. Only one of these 59 individuals had a blood lead >40 μg/dl, and none exceeded 50 μg/dl.

A weaker correlation was obtained between ALAD activity and distance from the smelter, this being due almost entirely to the female subjects. Examination of ALAD activity for males showed it to be similar regardless of distance from the smelter. The authors speculate that this could be caused by other lead exposures in the male population.

Two reports from the USSR describe effects of lead in an area near a smelter.[82,83] Average concentrations of lead in air were as high as 4.1 $\mu g/m^3$ at a distance of 1500 m; peak exposures at this distance reached 9.7 $\mu g/m^3$. Neurological disturbances were noted in 50 percent of the subjects from the smelter area, compared with 6 percent in controls. No data were given on age, sex, and type of disturbances.[82] In a later study, children from the area were found to excrete more coproporphyrin than controls and also more lead.[83] The highest lead concentration in urine was reported to be 50 μg/liter.

Studies of the effects of storage battery plants have been reported from France and Italy.[84,85] The French study found that children from an industrialized area containing such a plant excreted more ALA than those living in a different area.[84] Increased urinary excretion of lead and coproporphyrins was found in children living up to 300 ft from a battery plant in Italy.[85] Neither study gave data on plant emissions or lead in air.

These studies demonstrate that stationary sources within urban areas do contribute to increases in air lead levels. They show not only that mean exposure levels are higher but that the range of exposures encountered in their vicinities is much larger for daily or longer averaging times than in the vicinity of mobile sources. Increases of 2 to 3 $\mu g/m^3$ in air lead concentrations have been associated with higher blood lead levels in exposed populations.

Although the significantly higher air lead concentrations decrease rapidly with distance from the point of emission, they contribute, together with mobile emissions, to the generally higher air levels found in urban areas and thus to the higher blood lead levels found in urban populations.

12.3.1.3 URBAN POPULATION STUDIES

Another group of studies dealing with urban populations examined air lead and blood lead values without considering the specific sources of the lead in the air.[2,3,16,41,42] Azar et al.[3] obtained 24-hr air lead exposures for 150 males over a 2- to 4-week period using personal samplers. Study groups consisted of 30 men in each of 5 city-occupation categories. The subjects included cabdrivers, plant employees, and office workers. From two to eight blood samples were obtained from each subject during the air monitoring phase. Blood lead determinations were done in duplicate. Table 12-24 presents the geometric means for air lead and blood lead for the five groups. The geometric means were calculated by EPA from the raw data presented in the authors' report.[3]

TABLE 12-24. GEOMETRIC MEAN AIR AND BLOOD LEAD LEVELS (μg/100 g) FOR FIVE CITY-OCCUPATION GROUPS[3] (Data calculated by EPA)

Group	Geometric mean air lead. $\mu g/m^3$	GSD	Geometric mean blood lead. μg/100 g	GSD	Sample size
Plant employees Starke, FL	0.59	2.04	15.4	1.41	29
Plant employees Barksdale, WI	0.61	2.39	12.8	1.43	30
Cabdrivers Philadelphia, PA	2.59	1.16	22.1	1.16	30
Office workers Los Angeles, CA	2.97	1.29	18.4	1.24	30
Cabdrivers Los Angeles, CA	6.02	1.18	24.2	1.20	30

Regression equations calculated by the authors for members of each of the individual study groups revealed no slopes significantly greater than zero. In view of the rather narrow range of lead exposures observed within the groups, this result is not surprising. Examination of the slopes for each study group showed they were homogeneous and thus could be combined. The specific method of combination can be argued, however. Azar et al. chose to use dummy variables to represent the differing intercepts of the study groups because the intercepts were not homogeneous. In effect, this means drawing a line with a pooled slope of 0.153 through the average blood lead concentration.

The Tepper and Levin[2] study, described in detail previously, included both air and blood lead measurements. Housewives were recruited from "locations in the vicinity of air monitors." Women included were >19 and <80 years of age, had no history of lead poisoning, and had not eaten wild game. Table 12-25 presents the geometric mean air and blood lead values obtained in the study, as calculated by EPA from the raw data. Geometric mean air lead values ranged from 0.17 to 3.39

μg/m^3, and geometric mean blood lead values ranged from 12.5 (1.31) to 20.6 (1.33) μg/dl.

TABLE 12-25. GEOMETRIC MEAN AIR AND BLOOD LEAD VALUES FOR 11 STUDY POPULATIONS[2] (Data calculated by EPA)

Community	Geometric mean air lead, μg/m^3	Blood lead, μg/dl GM	Blood lead, μg/dl GSD	Sample size
Los Alamos, NM	0.17	14.9	1.28	185
Okeana, OH	0.32	15.6	1.39	156
Houston, TX	0.85	12.5	1.31	186
Port Washington, NY	1.13	15.4	1.28	196
Ardmore, PA	1.15	18.0	1.38	148
Lombard, IL	1.18	13.9	1.27	146
Washington, DC	1.19	19.2	1.26	219
Rittenhouse, PA	1.67	20.6	1.33	136
Bridgeport, IL	1.76	17.6	1.27	146
Greenwich Village, NY	2.08	16.6	1.28	139
Pasadena, CA	3.39	17.5	1.31	194

Nordman reported a population study from Finland[16] in which data from five urban and two rural areas were compared. This study was described in detail above. Air lead data were collected by stationary samplers. All levels were comparatively low, particularly in the rural environment, where a concentration of 0.025 μg/m^3 was seen. Urban-suburban levels ranged from 0.43 to 1.32 μg/m^3.

A study was undertaken by Tsuchiya et al.[41] in Tokyo using male policemen who worked, but not necessarily lived, in the vicinity of air samplers. In this study, five zones were established, based on degree of urbanization, ranging from central city to suburban. Air monitors were established at various police stations within each zone. Air sampling was conducted from September 1971 to September 1972; blood and urine samples were obtained from 2283 policemen in August and September 1971. Findings are presented in Table 12-26. A consistent correlation between air and blood lead means for the five zones is shown.

TABLE 12-26. MEAN AIR AND BLOOD LEAD VALUES FOR FIVE ZONES IN TOKYO STUDY[41]

Zones	Air lead, μg/m^3	Blood lead, μg/100 g
1	0.024	17.0
2	0.198	17.1
3	0.444	16.8
4	0.831	18.0
5	1.157	19.7

Goldsmith[42] obtained data for elementary school (9- and 10-year-olds) and high school students in 10 California communities. Lowest air lead exposures were 0.28 μg/m^3 and highest were 3.4 μg/m^3. For boys in elementary school, blood lead levels ranged from 14.3 to 23.3 μg/dl; those for girls ranged from 13.8 to 20.4 μg/dl for the same range of air lead exposures. The high school student population was made up of only males from some of the 10 towns. The air lead range was 0.77 to 2.75 μg/m^3 and the blood lead range was from 9.0 to 12.1 μg/dl. For the high school students the town with the highest air lead value did not have the highest blood lead level. A further comment on methodology pertains to the fact that a considerable lag time occurred between the collection and analysis of the blood samples.

12.3.1.4 CLINICAL AND EXPERIMENTAL STUDIES IN RELATION TO AIR LEAD/BLOOD LEAD RATIOS

Griffin and his colleagues undertook two studies using volunteers exposed in a gas chamber to an artificially generated aerosol of submicron-sized particles of lead dioxide.[86] All volunteers were introduced into the chamber 2 weeks prior to the initiation of the exposure; the lead exposures were scheduled to last 16 weeks, although the volunteers could drop out whenever they wished. Twenty-four volunteers, including 6 controls, participated in the 10.9 μg/m^3 exposure study. Twenty-one subjects, including 6 controls, participated in the 3.2 μg/m^3 exposure study. Not all volunteers completed the exposure regimen. Blood lead levels were found to stabilize after approximately 12 weeks. Among 11 men exposed to 10.9 μg/m^3 for at least 60 days, a stabilized mean level of 34.5 ± 5.1 μg/dl blood was obtained, as compared with an initial level of 19.4 ± 3.3 μg/dl. All but 2 of the 14 men exposed at 3.2 μg/m^3 for at least 60 days showed increases and a stabilized level of 25.6 ± 3.9 μg/dl was found, compared with an initial level of 20.5 ± 4.4 μg/dl. This represented an increase of about 40 percent above the base level.

From the data Table 12-27 was constructed, which shows the time needed to reach specific blood lead levels at the two air lead concentrations. As can readily be seen even at the lower exposure, it takes only 7 weeks for the population mean blood level to increase by 5 μg/dl.

In the article, the authors described both the chemistry and particle size of the lead aerosols generated. In general, the aerosols used in this experiment were somewhat less complex chemically, as well as somewhat smaller, than those found in the ambient environment. Griffin et al.,[86] however, point out that good agreement was achieved on the basis of the comparison of their observed blood lead

TABLE 12-27. LENGTH OF TIME NEEDED FOR MEAN BLOOD LEAD VALUES TO REACH SPECIFIED LEVELS AT TWO EXPOSURE LEVELS

Exposure group	Air lead level, μg/m^3	Avg. baseline blood lead level, μg/dl	Target blood lead level, μg/dl	Time needed to reach target level, wk
1	10.9	20.0	25	1 to 2
1	10.9	20.0	30	4
1	10.9	20.0	35	6
2	3.2	20.8	25	7
2	3.2	20.8	30	Not reached
2	3.2	20.8	35	Not reached

levels with those predicted by Goldsmith and Hexter's equation,[87] that is, $\log_{10}$ blood lead = 1.265 + 0.2433 $\log_{10}$ atmospheric exposure.

In contrast to the study of Griffin et al. that approximates the exposure regimen of environmentally exposed persons, Kehoe studied long-term exposures under conditions approximating those of occupationally exposed individuals.[88] Kehoe exposed a subject to an air lead as the sesquioxide first at 75 μg/m^3 then at 150 μg/m^3. Definite increases in urinary and blood lead levels emerged under each exposure. There appeared to be a plateau reached in the blood lead levels upon a steady state exposure.

Gross compiled data from lead balance studies conducted by Kehoe between 1934 and 1972 and determined that increases of levels in blood, urine, and feces under controlled clinical exposure were 0.38 μg/dl, 0.88 μg/day, and 2.50 μg/day, respectively, for each increase of 1 μg/m^3 in air lead levels.[89]

The derivation of these estimates is currently unknown but was based on the results of ingestion and inhalation studies carried out on 16 individuals over 21,000 person-days. During this period, there were 102 study periods for the 16 subjects. None of the subjects experienced harmful effects as a result of the lead exposures, the highest of which were approximately 30 μg/m^3 on a 24-hr basis (every other day to 6 days per week) for study periods up to 628 days. With a single exception, in none of the subjects did the blood level exceed 40 μg/dl.

Rabinowitz and colleagues have conducted studies of lead metabolism by stable isotopes that permit the determination of blood/air lead relationships.[90,91] In one study, a single volunteer was confined in a hospital's metabolic research ward for a period of 109 days for 23 hr a day.[90] He was then removed into a "clean" room in which the air was filtered to remove the particulate lead. For the first 15 days in the room, his daily lead intake was supplemented by lead additions to the diet to compensate for the loss of air lead intake. At the end of this 15-day period the dietary lead supplement was discontinued. He immediately showed a declining blood lead level that eventually reached a minimum. He then left the "clean" room and his blood lead level went back up. Unfortunately, his blood lead did not stabilize after his exit from the "clean" room.

A further report presents data, involving additional volunteers, from which a blood to air lead ratio can be derived.[91] Subsequent to a stabilizing period in a metabolic ward, they entered the filtered air room and blood lead levels decreased. The blood lead levels did stabilize upon exit from the clean room.

Chamberlain et al.[92,93] reported on studies in which gasoline containing tetraethyl lead labeled with ^{203}Pb was burned in an internal combustion engine and the resulting tagged lead exhaust aerosol was inhaled by 6 volunteers. The lead concentration[92] was typically about 6 mg/m^3 and the total particulate 30 mg/m^3. The aggregates of particles about 0.6 μm in diameter were stable; those $\leq$ 0.01 μm tended to coagulate. Exposures were for 30 min or less, and the progress of the lead through the body was monitored. It was found that about 40 percent of the particles was retained, and that 60 percent was exhaled. The lung clearance rate for ^{203}Pb activity varied markedly, depending on whether the aerosol was irradiated. The transference of activity to the blood peaked at 50 hr after inhalation at 48 percent of the initial lung burden. At 72 hr, about half of the lead had been removed to bone and other tissues and the other half had become attached to red cells. The amount of ^{203}Pb in the blood was found to decline with a biological half life of 16 days.

Chamberlain et al. then extrapolated these high-level, short-term exposures to longer term ones. The following formula and data were used to calculate a blood-to-air level ratio:

$$\alpha = \frac{[T_{1/2}]\,[\%\ \text{Deposition}]\,[\%\ \text{Absorption}]\,[\text{Daily ventilation}]}{[\text{Blood volume}]\,[0.693]} \qquad (12\text{-}7)$$

where: α = blood to air lead ratio

$T_{1/2}$ = biological half life

Data used were:

1. Airborne level = 1 $\mu g/m^3$
2. Exposure = 24 hr/day
3. Daily ventilation = 15 m^3/day
4. % Deposition = 40*
5. % Absorption = 50*
6. Blood volume = 5400 ml

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*These values were determined experimentally in this study; all others are authors' assumptions.

Using the above equation and values, Chamberlain et al.[93] obtained a ratio of 1.2, in contrast to a value of 1.1 reported in an earlier report,[92] where slightly different assumptions were made. In this earlier report,[92] data from Kehoe[88] and Williams et al.[94] were used in a similar manner to calculate ratios of 1.1 and 1.1, respectively. It is interesting to note the difference in the ratios calculated by Gross[89] and Chamberlain et al.[92] from the Kehoe data. However, the extrapolation of Chamberlain et al. of the short-term to long-term exposure is in close agreement with the results of Kehoe and of Williams et al., as Chamberlain et al. calculated them.

Chamberlain's ratios have been recalculated by Bridbord[95] on the basis of a more active person's daily ventilation of 20 m^3. This, he states, would yield a ratio of 1.6 $\mu g/dl$ for each 1 $\mu g/m^3$ of air lead exposure.

12.3.1.5 BLOOD/AIR LEAD RELATIONSHIPS

Summarization of the relationship between lead in air and lead in blood requires the consideration of several distinct lines of evidence. These include: the minimal air lead concentration at which blood lead levels are first elevated, the form and magnitude of the relationship, the proportion of the population whose blood lead level exceeds any specific value at any given air lead concentration, and whether the form or magnitude of the relationship varies depending on whether the air lead exposure is increasing, remaining constant, or decreasing.

On the first point, only a few studies have sufficiently precise estimates of air lead exposures to permit this calculation, namely Yankel et al.[1] and Azar et al.[3] EPA used William's [96] test on the data from both these studies to determine the air lead levels at which blood lead levels were found to be significantly higher than the geometric mean blood lead levels of the groups exposed to the lowest air lead level, which thus served as controls. William's test is a multiple comparison test designed to make such comparisons.

For data from the Yankel et al. study,[1] EPA pooled the lowest two air lead exposure areas (V and VI) to form the control group.

The test showed that area IV was the first, in the ordered data, that showed significant elevation of blood lead values. The corresponding air lead concentration for this area was 1.7 $\mu g/m^3$.

EPA, using this same test for the Azar et al. study,[3] showed that blood lead values for the Philadelphia cabdrivers were significantly different from that for the pooled Starke and Barksdale plant employees that constituted the control population. Blood lead values for the Los Angeles office workers were also significantly higher than those of control populations. The corresponding air lead exposures were 2.6 and 3.1 $\mu g/m^3$, respectively.

The clinical study of Griffin et al.[86] provides data that support the results of the EPA analysis of Azar et al.[3] data. The data show that individuals exposed to 3.2 $\mu g/m^3$ had a definite increase in their blood leads as a result of this exposure.

Thus, the available data are consistent as to the value of air lead concentration at which blood lead levels begin to increase. The Yankel et al. data[1] demonstrated this increase at 1.7 $\mu g/m^3$; the Azar et al. data,[3] at 2.6 $\mu g/m^3$. These results are not inconsistent because the Azar et al. study did not have a population exposed to a level of air lead between 1 and 2.6 $\mu g/m^3$.

The derivation of the functional relationship between air lead exposure and blood lead levels has technical difficulties because the true form of this relationship is not linear. No matter what the difficulty in making this assessment is, the form of the relationship is extremely important because it is used to determine the effect of a change in the blood lead levels as a function of the air lead values.

Some studies, by the very nature of their design, only permit calculating the ratio between a change in blood lead and associated change in the air lead concentration. For these situations, the calculated ratio can be considered as an estimate of the average ratio over the range of the air lead levels encountered.

For those studies in which a functional relationship can be derived, this ratio can be estimated for a given air lead concentration by evaluating the derivative of the functional relationship at that value. This ratio is subject to considerable change over the range of air lead levels encountered, depending on the form of the relationship that was fitted. We have chosen, wherever possible, to use the author's own model for the relationship.

The earliest attempt to use epidemiological data to calculate a blood-to-air lead relationship was made by Goldsmith and Hexter.[87] A linear regression equation of the logarithm of the blood lead level on the air lead level was performed on data from the Three-City Study.[40] Data from Kehoe's observations on 4 individuals experimentally exposed to 10 and 150 $\mu g/m^3$ in a pattern equivalent to a normal work exposure were found to fit the equation. The slope of this line was not significant below 2 $\mu g/m^3$ of air exposure, possibly because few observations were available in the Three-City Study below that level. The derived slope of the regression line suggests an increase of 1.3 $\mu g/dl$ for each microgram of air lead.

Azar et al.[3] used a log-log model to fit their data; the data, as well as the regression line, are presented in Figure 12-8. The slopes, that is, the ratios, were calculated from the equation, log Pb-B = 1.2557 + 0.153 (log Pb-A), at the four air lead values shown in Table 12-28. These slopes ranged from 2.6 at an air lead of 1.0 $\mu g/m^3$ to 0.7 at an air lead of 5.0 $\mu g/m^3$. It is important to note that all four air lead concentrations of interest are well within the range of the air levels observed.

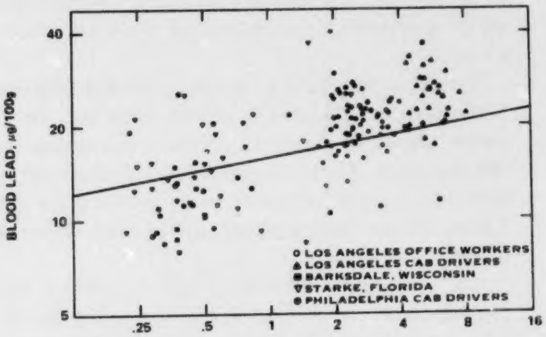

Figure 12-8. Blood lead versus air lead for urban male workers.[3]

TABLE 12-28. ESTIMATED BLOOD LEAD TO AIR LEAD RATIOS FOR FOUR AIR LEAD CONCENTRATIONS

Study	Population	Sample size	Ratio at air lead concentrations, µ. g/m³			
			1.0	2.0	3.5	5.0
Epidemiological						
Azar[a]	Adult males	149	2.57	1.43	0.89	0.66
Tepper-Levin[b]	Adult females	1908	0.87	0.92	1.00	1.08
Nordman[b]	Adult males	536			(0.42)[d]	
Nordman[b]	Adult females	478			(0.11)	
Fugas[b]	Adults	330			(2.64)	
Johnson[b]	Adult males	64			(0.80)	
Johnson[b]	Adult females	107			(0.60)	
Tsuchiya[b]	Adult males	591			(3.84)	
Goldsmith[b]	Children males	202			(2.30)	
Goldsmith[b]	Children females	203			(1.70)	
Yankel-von Lindern[a]	Children	879	1.16	1.21	1.27	1.37
Chamberlain[c]-Williams	Adults	482			(1.10)	
Daines[b]	Black females	(unknown)			(2.30)	
Clinical						
Griffin[b]	Adult males	11 @ 10.9			(1.40)	
Griffin[b]	Adult males	14 @ 3.2			(1.65)	
Rabinowitz[b]	Adult males	2			(1.7, 2.5)	
Gross[c]	Adults	(21,000 person-days)			(0.38)	
Chamberlain[c]	Adults	7			(1.20)	
Chamberlain[c]-Kehoe	Adults	5			(1.10)	

[a] Authors' regression equation evaluated at specific air lead.
[b] EPA calculation.
[c] Authors' calculations.
[d] Ratios presented in parentheses are not calculated from any regression equation.

One of the authors, Snee,[50] has since reanalyzed the data using a more complicated model for the relationship. His newer model attributes less of the increase in blood lead to air lead exposures and more to geographic area differences. The improvement in fit by use of this newer model is insignificant. Furthermore, in the new model, the area differences are correlated with the air lead differences. For these reasons, the original model is believed to be more appropriate for estimating the total effect of air lead.

Yankel et al.[1] used a log-linear model (Equation 12-6) to fit their data. The slopes of the four air lead values shown in Table 12-28 were calculated from this equation. These ranged from 1.2 at an air lead level of 1.0 $\mu g/m^3$ to 1.4 at an air lead of 5.0 $\mu g/m^3$. Again, all air lead concentrations were within the range of the data.

One assumption inherent in the calculation of the regression of blood lead on air lead using standard least squares is that the air lead values have been measured with no error. Unfortunately, this assumption is not correct. Obviously, the monitored air lead values are not the exact values inhaled by the subjects in the exposure area. The effect of measurement error in the independent variable is discussed by Kendall and Stuart.[97] In general, the calculation regression coefficients are underestimates of the true values. If either the error in the dependent variable, or the error in the independent variable, or the ratio of the two errors were known, then improved estimates could be calculated.

The Yankel et al. study[1] gives sufficient information to estimate the effect of this problem. The authors assigned 1 of 33 different estimated exposure levels to each individual in the study. If the within level variances of blood lead values are pooled for these 33 levels, the result is a pooled GSD of 1.28. Using the value of 1.28 for the error in the dependent variable, the regression coefficient of 0.041 reported by Yankel and von Lindern becomes 0.052. This adjustment increases the estimated blood lead to air lead ratio from 1.21 to 1.44 at 2 $\mu g/m^3$ and from 1.37 to 1.69 at 5 $\mu g/m^3$.

This problem may exist in some of the other studies, but it is not a serious problem in two of the other more important studies. In the Azar study,[3] personal samplers were used, so that individual exposures were measured more accurately than in any other epidemiologic study. In the Griffin study the air lead levels were controlled extremely closely, so that there was almost no variation in the exposure value.

The reanalysis of the Tepper-Levin study[2] as reported by Hasselblad and Nelson[22] was used to estimate the relationship of air lead to blood lead levels. A log-linear model was used that allowed for age and smoking differences, as well as the air lead exposure. This form of the model was chosen because it gave a better fit to the data than did the log-log model. The slopes were calculated from the log-linear model at the four air lead values shown in Table 12-28. These slopes ranged from 0.9 at an air lead of 1.0 $\mu g/m^3$ to 1.1 at an air lead of 5.0 $\mu g/m^3$. The air lead values only ranged from 0.2 to 3.4 $\mu g/m^3$, however.

Daines et al. reported two studies examining variations in blood lead ratios with distance from busy highways.[52] The studies were conducted in Camden, New Jersey, and involved black females. Only one of these studies can be used to determine the blood lead/air lead ratio because no air lead data were reported for the other study. In this study, blood lead levels of black females living in residences that were 3.7, 38.1, and 121.9 m distant from the highway were determined. Yearly mean air and blood lead levels for these three groups are presented in Table 12-29. From these values a ratio may be calculated as follows:

$$\text{ratio} = \frac{23.1-17.6}{4.60-2.24} = 2.3 \text{ for the total population.}$$

Using a similar calculation, housewives were found to have a ratio of 3.

TABLE 12-29. YEARLY MEAN AIR AND BLOOD LEAD LEVELS OF BLACK FEMALES IN RELATION TO DISTANCE OF RESIDENCE FROM A BUSY HIGHWAY

Study area	Distance from highway, m	Air lead, $\mu g/m^3$	Blood lead, $\mu g/100\,g$
Area A	3.7	4.60	23.1
Area B	38.1	2.41	17.4
Area C	121.9	2.24	17.6

In Yugoslavia, Fugas et al. in the study described earlier,[69] estimated the weekly time-weighted air lead exposures of eight population groups. The estimates were based on air lead values monitored at various locations and estimated proportions of time the individuals spent at those locations. The time-weighted exposure estimates, sample sizes, and blood lead levels for this study were presented earlier (Table 12-22). A weighted regression analysis was chosen for these data because the sample sizes of the customs officers and policemen varied from those for the other groups. The range of air leads was from 0.079 to 3.0 $\mu g/m^3$. The resulting slope is 2.64, and is presented in Table 12-28.

Snee[50] has criticized the inclusion of the streetcar drivers because of differences in social status and habits from the other groups. The effect of removing these subjects would be to reduce the calculated slope. This group was not removed because the air lead exposure was more precisely estimated than in other studies.

Data on Tokyo policemen reported by Tsuchiya et al.[41] and discussed in detail previously in this chapter may also be used to calculate a slope. Unfortunately, the slope that is derived can only be looked upon as confirmatory evidence and not as additional evidence because of the time difference between sampling the air and sampling the blood. Another possible complicating factor is the rural-urban gradient that parallels the air lead concentrations. Weighted regression analysis was used on the blood and air lead data reported in Table 12-26. The estimated slope is 3.8 and is recorded in Table 12-28. The observed range in air lead concentrations was 0.024 to 1.157 μg/m³.

From the Johnson et al. study in California,[6] estimates of the ratio between blood and air lead levels can be derived. Because of analysis problems encountered in the blood lead determinations of children, it was decided that a valid estimate could not be derived. Therefore, only data for adults will be treated here. It was decided to pool the data for adults and present separate ratios for males and females aged 17 and above. Geometric mean blood lead levels were used in the calculation because the blood lead data were found to follow a log-normal distribution.

For males, the pooled geometric means were 15.5 and 11.0 μg/dl for Los Angeles and Lancaster, respectively. For females, the corresponding values are 12.1 and 8.4 μg/dl. The ratio was calculated as follows for males: ratio = (15.5-11.0)/(6.3-0.6) = 0.8. The ratio for females was 0.6. These values are tabulated in Table 12-28.

Nordman in his doctoral dissertation[16] reported on blood and air lead levels for several populations in Finland (Table 12-30). Because of the large variation in the sample sizes for these populations, EPA calculated a weighted regression equation. The slope of the equation was estimated for both males and females separately and is 0.4 and 0.1, respectively, as presented in Table 12-28. It should be noted that the range of air lead concentrations covered by this study was 0.025 and 1.32 μg/m³.

Data from Goldsmith[42] on elementary and high school children in a number of California towns can also be used in the calculation of the slopes. EPA has separately analyzed the raw data from this study for elementary school males and females. The results of these analyses show ratios of 2.30 and 1.70, respectively (Table 12-28).

TABLE 12-30. BLOOD AND AIR LEAD LEVELS BY SEX IN FINNISH POPULATION STUDY[16]

Group	Air lead, μg/m³	Male blood lead, μg/dl			Female blood lead, μg/dl		
		N	Avg	SD	N	Avg	SD
Pertummaa	0.025	243	12.1	4.5	256	9.6	3.5
Pyhajarui	0.025	—	—	—	93	8.6	2.5
Suburban	0.74	37	10.6	2.8	81	9.7	2.6
Downtown	0.90	142	11.4	3.3	37	8.5	2.0
Policemen	1.32	28	13.5	2.8	—	—	—
Street sweepers	1.32	86	13.3	4.1	11	10.4	3.0

Chamberlain et al.[92] analyzed the data of Williams et al.[96] on occupationally exposed persons using personal monitors. Chamberlain adjusted the occupational exposures to 24-hr exposures by calculating the elevation in blood lead from a nonexposed population. He calculated a slope of 1.1.

Clinical studies also provide data useful in quantitating the relationship between blood and air lead. Griffin et al.,[86] in their clinical study of the largest number of subjects to date, exposed individuals to 2 levels of air lead concentrations, 10.9 and 3.2 μg/m³. The study design, it was believed, precludes fitting an overall equation to these data, and a separate calculation of a ratio is presented for the two experiments. In both experiments, the background air lead levels were estimated to be 0.15 μg/m³. In the 3.2 μg/m³ air lead exposure, the men increased their mean blood lead levels from 20.5 to 25.6 μg/dl. This yields a ratio of 1.65 (25.6-20.5)/(3.2-0.15). The 10.9 μg/m³ air lead exposure resulted in an increase of blood lead levels from 19.4 to 34.5 μg/dl. This gives a ratio of 1.40 (34.5-19.4)/(10.9-0.15). These values are shown in Table 12-28.

Chamberlain et al.[92] reanalyzed the Kehoe results by adjusting the 37.5-hr exposures per week to a 24-hr equivalent. They used data from 5 subjects whose 24-hr equivalent exposures ranged from 0.6 to 73.5 μg/m³. The calculated ratios ranged from 0.6 to 2.0, with an overall mean of 1.1 for the data.

In contrast to the analysis of Kehoe's work by Chamberlain in which a 1.1 ratio was calculated, Gross[89] reports a ratio of 0.38 for these data. At this time, no details are available concerning his methods. Therefore, the apparent discrepancy between these two analyses cannot be evaluated.

Chamberlain et al.,[92,93] as discussed earlier, calculated ratios of 1.1 and 1.2 based on the extrapolation of a short-term exposure to a long-term one. The calculation involves a number of experimentally determined as well as assumed numbers.

As described previously, Rabinowitz et al.[91] studied three individuals for metabolic changes in blood lead as a function of changes in the air lead concentration. In contrast to the other clinical studies described wherein air lead levels were increased, in this study the subjects were placed in a "clean room" in which the air was filtered. This study, therefore, pertains to the situation in which the air lead concentration has decreased. The blood lead levels were determined from the stabilized mean both when the subject was breathing normal as well as filtered air. One of the men did not have a stabilized blood lead after returning to breathing normal air; therefore, he could not be used in determining the ratio. The relevant data for calculating the ratio are included in Table 12-31.

TABLE 12-31. BLOOD AND AIR LEAD DATA FROM CLINICAL STUDY[91]

	Estimated air lead		Blood lead	
Subject	Normal air, μ g/m^3	Filtered air, μ g/m^3	Normal air, μg/100 g	Filtered air, μg/100 g
D	0.91	0.072	20.2	18.8
E	0.91	0.072	16.3	14.2

The calculation for subject D was done as follows: ratio = (20.2-18.8)/(0.91-0.072) = 1.7. The calculation for subject E results in a ratio of 2.5.

Only one data set (Azar et al.[3]) is available on which to estimate a dose-response relationship, that is, the proportion of a population exceeding a specified blood lead level for any specific exposure. The reasons for the paucity of data are twofold: (1) access is needed to the raw data and (2) the exposure data should be relatively precise.

The regression equation for the Azar study[3] has already been discussed. The mean square error (MSE) about this equation was calculated for all five areas combined. From the MSE, estimates of the percentage of the population exceeding a given blood lead level for a given air lead level are given by:

$$\text{Percent} = 100\left\{1 - N\left[\frac{\log_{10}(\text{blood lead}) - 1.2257 - 0.1531\log_{10}(\text{air lead})}{\text{MSE}^{1/2}}\right]\right\}$$

where: N(x) is the cumulative normal integral of a standard normal variable up to the point x. These percentages are given in Table 12-32 for a range of air lead values.

These tabulated percentages may not be representative of the general population, since they are based on a single study of 149 subjects. They are presented because they are the best estimates available of a dose-response relationship.

TABLE 12-32. ESTIMATED PERCENTAGE OF POPULATION EXCEEDING A SPECIFIC BLOOD LEAD LEVEL IN RELATION TO AMBIENT AIR LEAD EXPOSURE[a]

	Percent exceeding blood lead level of:		
Air lead, μg/m^3	20.0 μg/dl	30.0 μg/dl	40.0 μg/dl
0.5	15.22	0.59	0.02
1.0	26.20	1.67	0.07
1.5	34.12	2.88	0.16
2.0	40.23	4.12	0.26
2.5	45.15	5.35	0.38
3.0	49.23	6.57	0.51
3.5	52.69	7.75	0.66
4.0	55.67	8.90	0.81
4.5	58.27	10.01	0.97
5.0	60.57	11.09	1.14
6.0	64.45	13.16	1.48
7.0	67.63	15.10	1.83
8.0	70.28	16.92	2.20

[a] Data derived from the equation of Azar et al.[3]

The last element in defining the relationship between lead in blood and lead in air is a discussion of the effect that varying the concentration of lead in air has on the blood lead levels. Most of the data previously presented have dealt with steady state or increasing air lead concentrations. This section will summarize the results of studies showing the effect of decreasing the concentration of lead in air on the blood lead levels of human populations.

Rabinowitz et al.'s study [91] provides estimated ratios for two subjects under carefully controlled conditions who experienced a decrease in their air lead concentrations. For the two subjects, a 1 μg/m^3 decrease in air lead levels resulted in a 2 μg/100 g decrease in blood lead levels.

Baker[98] presented data to the EPA Science Advisory Board showing decreases in blood lead levels in the vicinity of an Idaho smelter between 1974 and 1975 (Table 12-33). Information from all study areas combined indicated that blood lead levels had decreased by 2.3 μg/dl for each 1 μg/m^3 reduction in air lead. This same investigator provided additional information in a separate communication to EPA showing that, when analyses were limited to children of nonsmelter workers, blood lead levels decreased 2.0 μg/dl in all study areas for each decrease of 1 μg/m^3 of air lead. If the analyses included only those children of nonsmelter workers exposed to air lead levels ranging from 0.5 to 10

μg/m^3, blood lead levels decreased 1.3 μg/dl for each unit decrease in air lead and also showed a higher ratio at greater air lead concentrations. From these analyses, it seems apparent that a single ratio cannot describe the data from this study.

TABLE 12-33. COMPARISON OF BLOOD LEAD LEVELS IN CHILDREN WITH AIR LEAD LEVELS FOR 1974 AND 1975 (EPA analyses)

	Blood lead levels, μ g/dl			Air lead levels, μ g/m^3			
Study area	1974	1975	Diff.	1974	1975	Diff.	Pb-B diff./ Pb-A diff.
1	69	46	23	18	10.3	7.7	3.0
2	49	38	11	14	8.6	5.4	2.0
3	36	32	4	6.7	4.9	1.8	2.2
4	33	27	5	3.1	2.5	0.6	8.0

Data from Angle and McIntire's studies[73-76] in Omaha also provide data in this regard. They found blood lead levels of urban children, aged 6 to 18, to consistently decrease during the years 1970 to 1973. This decrease was almost 10 μg/dl across all study groups. Furthermore, this decrease has been found to be closely correlated with a decrease in air lead from about 1.5 to less than 0.5 μg/m^3. In a reanalysis of the full data base, Angle has calculated an overall equation of $\text{Pb-B} = 10.04\ (\text{Pb-A}) + 17.06$, $r = 0.95$.

Data from New York City analyzed by HUD[38] and described in detail in the demographic variability section of this chapter may also provide supportive data for the notion that a decrease in blood lead level is associated with decreased air lead exposure. In the New York lead screening program geometric mean blood lead values have been noted as decreasing consistently from 1970 to 1976. During this time, some changes occurred in the number of children sampled, so that the more recent years have far fewer data points than the earlier years. No significant break in the trend was observed as the change in sample size was noted. Data from one Hi-Vol air station provided continuous air lead values over this period in New York City. The air lead values measured there, not really representative of the exposure of the children being studied, have been following a similar pattern. It is also interesting to note that lead in gasoline in New York City was also being reduced during this period.

The quantitative estimates provided from the three studies discussed show decreasing air lead concentrations vary from a minimum of 1.3 to 8 or 10 μg/dl. These data suggest that a greater ratio may hold for decreases in air lead than for steady state or increasing exposures.

In summary, in all quantitative studies presented, a positive relationship between blood lead and air lead has been found. The form and magnitude of the relationship, however, has not been found to be constant but varies in the studies reviewed. Table 12-28 summarizes the quantitative estimates derived from the review and analysis of the literature.

In general, the data show that the blood lead to air lead ratio is not constant over the range of air exposure encountered (it varies in most studies between 1 and 2), that males appear to have higher ratios than females, and that children have a slightly higher ratio than adults. Also, the data suggest that more attention should be given to studies of decreasing air lead concentrations in that the ratios derived from such studies appear higher than those of steady state or increasing exposures.

12.3.2 **Soil and Dust Exposures**

The relationship of exposure to lead contained in soil and housedust and the quantity of lead in humans, particularly in children, has been the subject of scientific investigation for some time.[78,99-105] Duggan and Williams[105] have recently published an assessment of the risk of increased blood lead resulting from the ingestion of lead in dust. Some of these studies have been concerned with the effects of such exposures:[78,99-102] others have concentrated on the means by which the lead in soil and dust becomes available to the body.[103,104]

In one of the earliest investigations, Fairey and Gray conducted a retrospective study of lead poisoning cases in Charleston, South Carolina.[99] Two-inch core soil samples were collected from 170 randomly selected sites in the city and were compared with soil samples taken from the yards of homes where 37 cases of lead poisoning had occurred. The soil lead values obtained had a wide range, from 1 to 12,000 ppm, with 75 percent of the samples containing less than 500 ppm. A significant relationship between soil lead levels and lead poisoning cases was established; 500 ppm was used as the cutpoint in the chi-square contingency analysis. This study was the first to examine this complex problem and, although data support the soil lead hypothesis, they were not such as to allow for quantification of the relationship between soil lead and blood lead levels. Furthermore, because no other source of lead was measured, the association found might have been caused by confounding additional sources of lead, such as paint or air.

A later study by Galke et al., also in Charleston, used a house-to-house survey to recruit 194 black preschool children.[43] Soil lead, paint lead, and air lead exposures as measured by traffic density were established for each child. When the population was divided into 2 groups based on the median soil lead value (585 μg/g), a 5-μg/dl difference in blood lead levels was obtained. Soil lead exposure for this population ranged from 9 to 7890 μg/g. A multiple regression analysis of the data showed that vehicle traffic pattern, when defined by area of recruitment (i.e., high or low); lead level in exterior siding paint; and lead in soil were all independently and significantly related to blood lead levels.

Barltrop et al.[100] described two studies in England investigating the soil lead to blood lead relationship. In the first study, children aged 2 and 3 and their mothers from two towns chosen for their soil lead content each had their blood lead level determined from a capillary sample. Hair samples were also collected and analyzed for lead. Lead content of the suspended particulate matter and soil was measured. Soil samples for each home were a composite of several 2-in. core samples taken from the yard of each home. Chemical analysis of the lead content of soil in the two towns showed a two- to threefold difference, with the values in the control town being about 200 to 300 ppm compared with about 700 to 1000 ppm in the exposed town. A difference was also noted in the mean air lead content of the two towns, 0.69 μg/m^3 compared with 0.29 μg/m^3, respectively. Although this difference existed, both air lead values were thought low enough not to affect the blood level values differentially. Mean surface soil lead concentrations for the two communities were statistically different, the means for the high and low community being 909 and 398 ppm, respectively. Despite this difference, no statistically significant differences in mothers' blood lead levels or children's blood or hair levels of lead were noted. There was, however, suggestive evidence of a difference in hair lead levels for children. Further statistical analysis of the data, using correlational analysis on either raw or log-transformed blood lead data, likewise failed to show a statistical relationship of soil lead with either blood lead or hair lead.

The second study was reported in both preliminary and final form.[100,101] In the more detailed report,[101] children's homes were classified by their soil lead content into three groups, namely <1,000, 1000 to 10,000, and >10,000 ppm. As shown in Table 12-34, children's mean blood lead levels increased correspondingly from 20.7 to 29.0 μg/dl. Mean soil lead levels for the low and high soil exposure groups were 420 and 13,969 ppm, respectively. Mothers' blood levels, however, did not reflect this trend; nor were the children's fecal lead levels different across the soil exposure areas.

TABLE 12-34. MEAN BLOOD AND SOIL LEAD CONCENTRATIONS IN ENGLISH STUDY[101]

Category of soil lead, ppm	Sample size	Children's blood lead, μ g/dl	Soil lead, ppm
<1000	29	20.7	420
1000-10000	43	23.8	3390
>10000	10	29.0	13969

Other studies have investigated the relationship of dust lead to absorption.[33,78,102,106] Some of these also included measurements of soil lead.

Lepow et al.,[106] for example, studied the lead content of air, housedust, and dirt, as well as the lead content of dirt on hands, food, and water, to determine the cause of chronically elevated blood lead levels in ten 2- to 6-year-old children in Hartford, Connecticut. Lead based paints had been eliminated as a significant source of lead for these children. Ambient air lead concentrations varied from 1.7 to 7.0 μg/m^3. The mean lead concentration in dirt was 1,200 μg/g and in dust, 11,000 μg/g. The mean concentration of lead in dirt on children's hands was 2,400 ppm. The mean weight of samples of dirt from hands was 11 mg, which represented only a small fraction of the total dirt on hands. Observation of the mouthing behavior in these young children lead to the conclusion that the hands-in-mouth exposure route was the principal cause of excessive lead accumulation in these children.

Angle et al.,[74] studying children in Omaha, Nebraska, found several interesting associations between soil or housedust lead concentrations and blood lead levels. In this report, three groups of children were compared: (1) suburban versus urban high school, (2) suburban versus urban 10- to 12-year-olds, and (3) black elementary school children with blood lead ≤ 20 versus ≥ 20. Air lead levels, all of which were less than 1 μg/m^3, were not shown to be related to blood lead levels. Soil and housedust were associated, although not always statistically significantly.

Creason et al.,[102] studying hair metal levels in the New York metropolitan area, used both dustfall and housedust as their exposure variables. Three geographic areas in metropolitan New York were chosen to represent an exposure gradient. Limited dustfall and housedust samples were taken to verify the gradient and to estimate its magnitude. Hair samples were collected from residents in locations enrolled in other air pollution studies. Mean total environmental and hair lead levels were then compared. Hair lead levels ranged from 12 μg/g in the low area to 17 μg/g in the high. Mean dustfall and housedust lead levels ranged from 2 to 16 mg/m^2-month, and from 279 to 766 μg/g, respectively. Hair lead levels in both children and adults were found to be significantly related to both dustfall and housedust lead. No attempt was made to determine the original source of these dusts. Further, the study design did not permit the establishment of which of the two dust types or both were the actual contributors to the hair lead levels. The investigators concluded that the primary cause of elevated blood lead levels in children was ingestion or inhalation of dust containing lead.

Two other studies, which were described in more detail in Section 12.3, can be used to examine the relationship of lead in soil and dust with lead in blood.[1,34] Yankel et al. showed that lead in both soil and dust was independently related to blood lead levels. In their opinion, 1000 ppm soil lead exposure was cause for concern. Reanalysis of the Dallas traffic study showed a significant slope of blood lead levels in relation to soil lead levels ($\beta = 0.0662$).[34] Lastly, Shellshear's case report from New Zealand ascribes a medically diagnosed case of lead poisoning to high soil lead content in the child's home environment.[107]

Two studies have investigated the mechanism by which lead from soil and dust gets into the body.[103,104] Sayre et al. in Rochester, New York, demonstrated the feasibility of housedust being a source of lead for children.[103] Two groups of houses, one inner-city and the other suburban, were chosen for the study. Lead-free sanitary paper towels were used to collect dust samples from house surfaces and the hands of children.[108] The medians for the hand and household samples were used as the cutpoints in the chi-square contingency analysis. A statistically significant difference between the urban and suburban homes for dust levels was noted, as was a relationship between household dust levels and hand dust levels.[106]

Ter Haar and Aronow[104] investigated lead absorption in children that can be attributed to ingestion of dust and dirt. They reasoned that because the proportion of the naturally occurring isotope ^{210}Pb varies for paint chips, airborne particulates, fallout dust, housedust, yard dirt, and street dirt, it would be possible to identify the sources of ingested lead. They collected 24-hr excreta from 8 hospitalized children for the first day of hospitalization. These children, 1 to 3 years old, were suspected of having elevated body burdens of lead, and one criterion for the suspicion was a history of pica. Ten children of the same age level, who lived in good housing in Detroit and the suburbs, were selected as controls and 24-hr excreta were collected for them. The excreta were dried and stable lead as well as ^{210}Pb content was determined. For seven hospitalized children, the stable lead mean value was 22.43 μg/g dry excreta, and the eighth child had a value of 1640 μg/g. The controls' mean for stable lead was 4.1 μg/g dry excreta. However, the respective means for ^{210}Pb expressed as pCi/g dry matter were 0.044 and 0.040. The authors concluded that because there is no significant difference between these means for ^{210}Pb, the hypothesis that young children with pica eat dust is not supported. However, all that the data, in fact, do show is that both groups of children were comparable as to the amounts of ^{210}Pb and vastly different in respect to stable lead per gram of dry excreta. The hospitalized children ingested larger amounts of material containing stable lead. Granting that the hospitalized children ingested leaded paint chips and the controls did not, does not permit the conclusion that all the ^{210}Pb found in all the children originated in food and that no dirt and dust was ingested by control children whereas hospitalized children ate only paint chips.

The data from all these studies can be summarized fairly succinctly. There is evidence that children can pick up lead from their environment by getting it on their hands. Duggan and Williams[105] have summarized the literature on the amounts of lead ingested by ingestion of dust. In their opinion, a quantity of 50 μg of lead is ingested daily by children by means of street dust. As yet there are no solid data directly demonstrating the next link, that is, transfer of dust and soil from hand to mouth. A clinical case report has indicated, however, that soil lead levels can lead to excessively elevated blood lead levels. Also, the data of Barltrop[101] and Galke et al.[43] indicate that soil lead exposures, often found in urban settings, can contribute between 5 and 8 μg/dl to the blood's lead burden.[33,101]

The consensus appears to be that observable increases in blood lead levels occur at soil or dust lead exposures of 500 to 1000 ppm. From the data available in the literature, a summary table (Table 12-35) was constructed by EPA. A regression analysis was used to relate the logarithm of the blood lead to the logarithm of the soil lead. From the regression, a coefficient, b, the mean percent age increase in blood lead for a two fold increase in soil lead, can be calculated:

$$\% \text{ increase} = 100\,[\exp(b/\log_e(2))] \quad (12\text{-}7)$$

TABLE 12-35. SUMMARY OF SOIL LEAD/BLOOD LEAD RELATIONSHIPS

Study	Age, years	Regression coefficient, log-log	Geom. mean blood lead, μg/dl	Geom. mean soil level, μg/g	Mean % increase in Pb-B for 2 x soil level
Charleston, SC[43]	1-5	0.0432	36.4	451.6	3.0
Kellogg, ID[1]	1-9	0.0528	37.5	1518.1	3.7
Dallas, TX[34]	1-5	0.0662	11.4	91.6	4.7
England[101]	2-3	0.0840	23.2	1849.1	6.0

Table 12-35 shows a surprising consistency in the percentage increase in mean blood lead levels for a twofold increase in soil lead levels (3 to 6 percent), given the wide diversity in populations studied and soil levels encountered. The Charleston study involved black preschool children living in the inner city with several additional known environmental sources of lead. The Idaho study was of a smelter site in a rural setting. Barltrop's data from England showed virtually no environmental source other than that from soil. The Dallas study was of a community that was relatively lead free. It is interesting to note that the larger estimates of the percentage increase in blood lead occurred in the children with the lowest blood lead levels.

12.3.3 **Food and Water Exposures**

In typical urban settings, food probably constitutes the body's largest direct source of lead because almost every item in the diet contains some measurable amount of the metal.

Three approaches have been used to estimate dietary intake of lead: duplicate meals, market basket surveys, and fecal lead determinations. The estimated dietary lead intake of Americans has decreased markedly since the presentation of Kehoe's data in the 1940's, which indicated, based on fecal lead determinations, that the daily intake was between 100 and 350 μg/day.[88] Most of the more recent comparable data[2,109,110] have reduced that estimate to between 50 and 150 μg/day. The California study of Johnson et al.[7] points to a daily intake of about 100 to 150 μg, such intake being similar for both rural and urban populations. Also, Chisholm and Harrison,[109] in a study of children aged 12 to 35 months, found a mean fecal excretion rate of 132 μg/day, and Barltrop and Killola a value of 130 μg.[110]

Much recent work has been concerned with the lead content of the market basket or total diet in which the content of foods meeting typical nutritional needs is analyzed. The foodstuffs are assembled in accordance with national food sample surveys. One such study[111,112] has indicated that the lead content of the diet of young adults averages 150 to 200 μg/day, and another[113] cites a figure of 254 μg/day for 15- to 20-year-old males. At least 30 percent of this amount in the latter study was attributed to the consumption of canned foods. Kolbye[111] and Mahaffey et al.[112] have suggested an average food-based intake of 80 to 100 μg of lead for children 12 to 35 months old. Additional studies in this field have been reviewed by Mahaffey.[112]

Despite the above estimates of dietary lead content, the quantitative relationship between dietary intake and blood lead levels is not well established; the bulk of the studies described in Chapter 10 that address this relationship, however, point to a sustained value of 6 μg/dl for 100 μg of dietary lead intake.

Water, itself, can also be a source of significant quantities of lead with the metal present in the supply itself. More frequent, however, is an increase in the quantity of particulate or dissolved lead as water is delivered from the treatment plant to the user through the lead pipes often found in older housing. Most natural waters contain only from 10 to 20 μg/liter of lead and most problems occur when lead piping is used in areas in which the drinking water is lead solvent; that is, it is soft and has a low pH.

Although the use of lead piping has been largely prohibited in recent construction, occasional episodes of poisoning from this lead source still occur. These cases most frequently involve isolated farms or houses in rural areas, but a surprising situation was revealed in 1972 when Beattie et al.[114,115] showed the seriousness of the situation in Glasgow, Scotland, which had very pure but soft drinking water as its source. They demonstrated a clear association between blood lead levels and inhibition of the enzyme ALAD in children living in houses with (1) lead water pipes and lead water tanks, (2) no lead water tank but with more than 60 ft of lead piping, and (3) less than 60 ft of lead piping. The mean lead content of the water as supplied by the reservoir was 17.9 μg/liter; that taken from the faucets of groups 1, 2, and 3 was 934, 239, and 108 μg/liter, respectively.

Another English study[116] showed a clear difference between the bone lead content of the populations of Glasgow and London, the latter having a hard, relatively nonsolvent water supply.

In a study of 1200 blood donors in Belgium,[117] persons from homes with lead piping and supplied with corrosive water had significantly higher blood lead levels.

In Boston, Mass., an investigation was made of water distributed via lead pipes. In addition to the data on lead in water, account was taken of socioeconomic and demographic factors as well as other sources of lead in the environment.[118,119] Participants, 771 persons from 383 households, were classified into age groups of <6, 6 to 20, and >20 years of age for analysis.[118] A clear association between water lead and blood lead was apparent (Table 12-36). For children under 6 years of age, 34.6 percent of those consuming water with lead above the U.S. standard of 50 μg/liter had a blood lead value ≥ 35 μg/dl, whereas only 17.4 percent of those consuming water within the standard had blood lead values of ≥ 35 μg/dl.

TABLE 12-36. BLOOD LEAD LEVELS OF 771 PERSONS IN RELATION TO LEAD CONTENT OF DRINKING WATER, BOSTON, MASS.[118]

	Persons consuming water (standing grab samples)				
	<50 μg Pb/liter		$\geq$50 μg Pb/liter		
Blood lead levels, μg/dl	No.	Percent	No.	Percent	Total
<35	622	91	68	77.3	690
$\geq$35	61	9	20	22.7	81
Total	683	100	88	100.0	771

χ^2 = 14.35; df = 1.
$P < 0.01$.

Greathouse et al. have published an extensive regression analysis of these data.[119] Blood lead levels were found to be significantly related to age, education of head of household, sex, and water lead exposure. Of the two types of water samples taken, standing grab and running grab, the former was shown to be more closely related to blood lead levels than the latter.

As noted in Chapter 10 of this document, roughly 10 percent of lead in solid foodstuffs is absorbed by adults; the corresponding value for liquids is about 50 percent. The relative risk for exposure to waterborne lead is, therefore, considerably greater.

12.3.4 Effects of Lead in the Housing Environment: Lead in Paint

A major source of environmental lead exposure for the general population comes from lead contained in both interior and exterior paint on dwellings. The amount of lead present, as well as its accessibility, depends upon the age of the residence (because older buildings are painted with paint manufactured before lead content was regulated) and the physical condition of the paint. It is generally accepted by the public and by health professionals that lead based paint is the major source of pediatric lead poisoning with clinical symptoms in the United States.[120]

The level and distribution of lead paint in a dwelling is a complex function of history, geography, economics, and the decorating habits of its residents. Lead pigments were the first pigments produced on a large commercial scale when the paint industry began its growth in the early 1900's. In the 1930's lead pigments were gradually replaced with zinc and other opacifiers. By the 1940's, titanium dioxide became available and has now become the most commonly used pigment for residential coatings. There was no regulation of the use of lead in house paints until 1955, when the paint industry adopted a voluntary standard that limited the lead content in paint, for interior uses, to no more than 1 percent by weight of the nonvolatile solids. At about the same time, local jurisdictions began adopting codes and regulations that prohibited the sale and use of interior paints containing more than 1 percent lead.[121]

In spite of the change in paint technology and local regulations governing its use, and contrary to popular belief, interior paint with significant amounts of lead was still available in the 1970's. A 1971 study in New York City found that 8 of 76 paints tested had a lead content ranging from 2.6 to 10.8 percent, well above the city's legally permissible 1 percent level.[122] Later studies by the National Bureau of Standards[123] and by the Consumer Product Safety Commission[124] showed a continuing decrease in the number of interior paints with lead levels greater than 1 percent. By 1974, only 2 percent of the interior paints sampled were found to have greater than 1 percent lead in the dried film.[124]

The level of lead in paint in a residence that should be considered a hazard remains in doubt. Not only is the total amount of lead in paint important, but also the accessibility by a child of the painted surface as well as the frequency of ingestion. Attempts to set an acceptable lead level, *in situ*, have been unsuccessful and preventive control of lead paint hazards has been concerned with levels of lead in paint currently manufactured. In one of its reviews, NAS concluded: "Since control of the lead paint hazard is difficult to accomplish once multiple layers have been applied in homes over two to three decades, and since control is more easily regulated at the time of manufacture, we recommend that the lead content of paints be set and enforced at time of manufacture."[125]

Legal control of lead paint hazards is being attempted by local communities through health or housing codes and regulations. At the Federal level, the Department of Housing and Urban Development has issued regulations for lead hazard abatement in housing units assisted or supported by its programs. Generally, the lead level considered hazardous ranges from 0.5 to 2.5 mg/cm^2, but the level of lead content selected appears to be dependent more on the sensitivity of field measurement by different regulatory bodies (using X-ray fluorescent lead detectors) than on direct biological dose-response relationships. Regulations also require lead hazard abatement when the paint is loose, flaking, peeling, or broken, or in some cases when it is on surfaces within reach of a child's mouth.

Some studies have been carried out to determine the distribution of lead levels in paint in residences. A survey of lead levels in 2370 randomly selected dwellings in Pittsburgh provides some indication of the lead levels to be found.[126] Figure 12-9 shows the distribution curves for the highest lead level found in dwellings for three age groupings. The curves bear out the statement often made that paint with high levels of lead is most frequently found in pre1940 residences. One cannot assume, however, that high level lead paint is absent in dwellings built after 1940. In the case of the houses surveyed in Pittsburgh, about 20 percent of the residences built after 1960 have at least one surface with more than 1.5 mg/cm^2 lead.

The distribution of lead within an individual dwelling varies considerably. Figure 12-10 presents the distribution of the highest paint lead measurements on walls, doors, and windows for all the buildings sampled. These data show that the lead is not uniformly distributed throughout the units. Lead paint is most frequently found on doors and windows where lead levels greater than 1.5 mg/cm^2 were found on 2 percent of the surfaces surveyed, whereas only about 1 percent of the walls had lead levels greater than 1.5 mg/cm^2.[126]

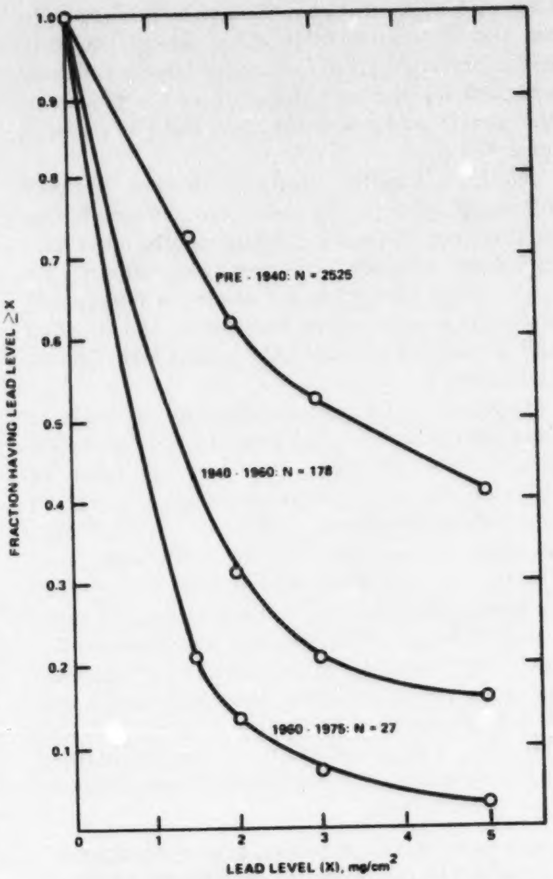

Figure 12-9. Cumulative distribution of lead levels in dwelling units.[126]

The literature[120] generally accepts the premise that the presence of lead in paint is a necessary but not sufficient condition for a hazard to be present. Accessibility in terms of peeling, flaking, or loose paint is also a necessary condition for the presence of a hazard. Figure 12-11 shows the distribution of lead levels and nonintact conditions for dwellings and surfaces for the Pittsburgh sample. Of the total samples surveyed, about 14 percent of the residences would have accessible paint with a lead content greater than 1.5 mg/cm^2.

It is not possible to extrapolate the results of the Pittsburgh survey nationally; however, additional data from a pilot study of 115 residences in Washington, D.C., showed similar results.[127]

An attempt was made in the Pittsburgh study to obtain information about the correlation between

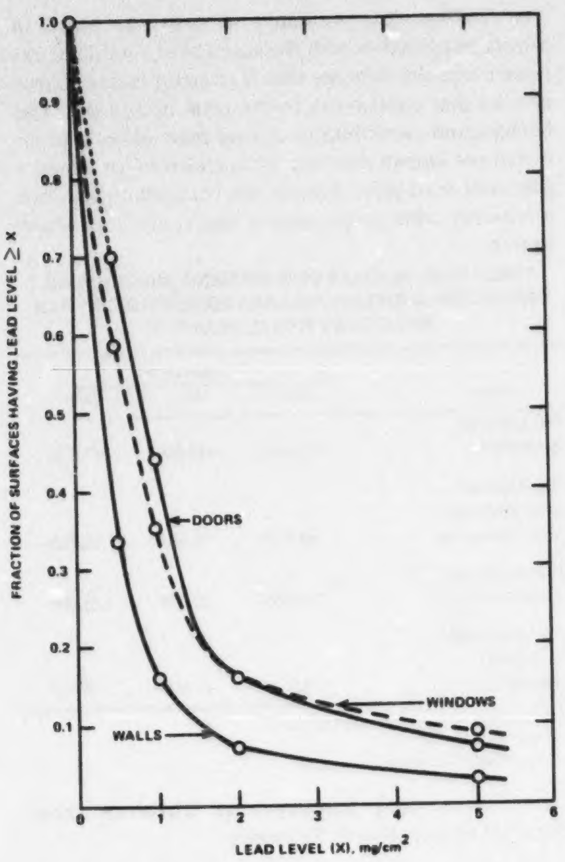

Figure 12-10. Cumulative distribution of lead levels by location in dwelling, all ages.[126]

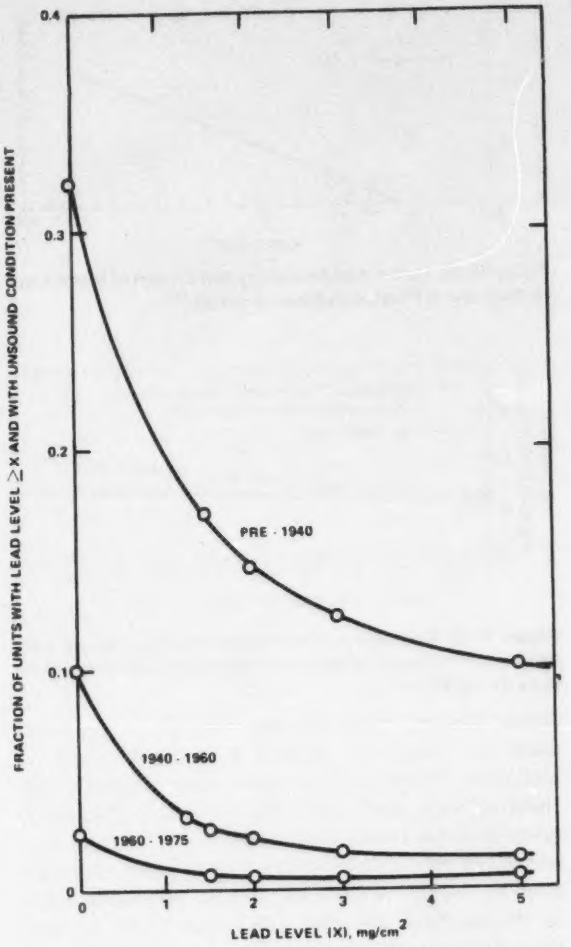

Figure 12-11. Cumulative distribution of lead levels in dwelling units with unsound paint conditions.[126]

the quantity and condition of lead paint in buildings and the blood lead of children who resided there.[128] Blood lead analyses and socioeconomic data for 456 children were obtained along with the information about lead levels in the dwelling. Figure 12-12 shows the cumulative distribution of the blood lead levels for this group. Figure 12-13 is a plot of the blood lead levels versus the fraction of surfaces within a dwelling with lead levels of at least 2 mg/cm². Analysis of the data shows a low correlation between the blood lead levels of the children and fraction of surfaces with lead levels above 2 mg/cm², but a stronger correlation between the blood lead levels and condition of the painted surfaces in the dwelling in which children reside. This latter correlation appeared to be independent of the lead levels in the dwellings.

Two other studies have attempted to relate blood lead levels and paint lead as determined by X-ray fluorescence. Reece et al. in Cincinnati studied 81 children from two lower socioeconomic communities.[129] Blood leads were analyzed by the dithizone method. There was considerable lead in the home environment, but it was not reflected in the children's blood lead. Analytic procedures used to test the hypothesis were not described; neither were the raw data presented.

Galke et al. in their study of inner-city black children measured the paint lead, both interior and exterior, as well as soil and traffic exposure.[43] In a multiple regression analysis, exterior siding paint lead was found to be significantly related to blood lead levels.

Although most of the evidence indicates that the source of exposure in childhood lead poisoning is almost invariably peeling lead paint and broken lead-impregnated plaster found in poorly main-

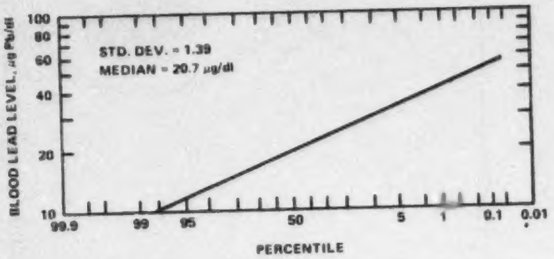

Figure 12-12. Cumulative frequency distribution of blood lead levels found in Pittsburgh housing survey.[128]

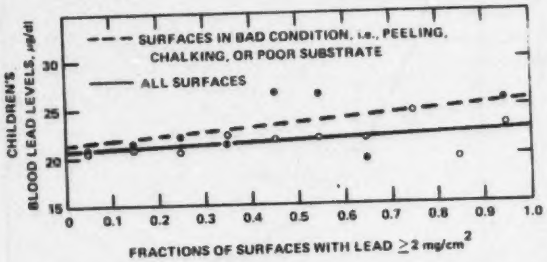

Figure 12-13. Correlation of children's blood lead levels with fractions of surfaces within a dwelling having lead concentrations ≥2 mg Pb/cm².

tained houses, there are also reports of exposure cases that cannot be equated with the presence of lead paint. Further, the analysis of paint in homes of children with lead poisoning has not consistently revealed a hazardous lead content.[120] For example, one paper reported 5466 samples of paint obtained from the home environment of lead poisoning cases in Philadelphia between 1964 and 1968. Among these 5466 samples of paint, 67 percent yielded positive findings defined as paint with more than 1 percent lead.[130]

Data published or made available by the Center for Disease Control, Department of Health, Education, and Welfare, also show that a significant number of children with undue lead absorption occupy buildings that were inspected for lead-based paint hazards, but in which no hazard could be demonstrated.[131,132] Table 12-37 summarizes the data obtained from the HEW funded lead-based paint poisoning control projects for fiscal years 1974, 1975, and 1976, plus the transition quarter July 1, 1976 to September 30, 1976. These data show that in about 40 to 45 percent of confirmed cases of elevated blood lead levels, a possible source of lead paint hazard could not be located. The implications of these findings are not clear. They should not, however, weaken the role of lead-based paint as a major environmental source of lead for children. The findings are presented in order to place in proper perspective both the concept of total lead exposure and the concept that lead paint is one source of lead that contributes to the total body load. The background contribution of lead from other sources is still not known even for those children for whom a potential lead-paint hazard has been identified; nor is it known what proportion of lead came from which source.

TABLE 12-37. RESULTS OF SCREENING AND HOUSING INSPECTION IN CHILDHOOD LEAD POISONING CONTROL PROJECT BY FISCAL YEAR[131,132]

Results	Fiscal year[a]		
	1976[132]	1975[131]	1974[131]
No. children screened	500,463	440,650	371,955
No. children with elevated lead exposure	69,131[b]	28,597[c]	16,228[c]
No. dwellings inspected	50,276	30,227	23,096
No. dwellings with lead hazard	28,333	17,609	13,742

[a] Fiscal year 1976 includes transition quarter.
[b] CDC Classes II-IV.
[c] Confirmed blood lead level ≥40 μg/dl.

12.3.5 Secondary Exposure of Children from Parents' Occupational Exposure

Excessive intake and absorption of lead for children can result when a parent who works in a dusty environment with a high lead content brings dust home on his clothes, shoes, or even his automobile. Once home, this dust is then available to his children.

Excessive intake and absorption also can occur when children voluntarily ingest nonfood items, such as clay, plaster, or paint chips. This is the classical pica, which refers to the intentional ingestion of nonfood material rather than to the passive, nonintentional ingestion of dust from a dirty finger or piece of candy that has been dropped and thus contaiminated.

Landrigan et al.[62] reported that the 174 children of smelter workers who lived within 24 km of the smelter had significantly higher blood lead levels, a mean of 55.1 μg/dl, than the 511 children of persons in other occupations who lived in the same areas whose mean blood lead level was 43.7 μg/dl.

Analyses by EPA staff of the data collected in Idaho showed that employment of the father at the lead smelter, at a zinc smelter, or in the lead mine resulted in higher blood lead levels in the children living in the same house with such fathers than children whose fathers were employed in different locations (Table 12-38).

TABLE 12-38. GEOMETRIC MEAN BLOOD LEAD LEVELS (μg/dl) OF CHILDREN BY PARENTAL EMPLOYMENT (EPA analysis of 1974 data)

Age and study area	Lead smelter worker	Lead/zinc mine worker	Zinc smelter worker	Other occupation
1 to 3 years				
1	77.1(12)[a]	65.7(25)	66.3(11)	65.9(13)
2	56.8(11)	53.5(21)	55.1(6)	48.5(30)
3	33.7(6)	54.5(15)	32.3(2)	34.8(26)
4	29.6(4)	36.0(16)	41.7(4)	31.5(22)
5	—	31.8(29)	—	27.2(16)
6	—	—	—	22.4(34)
4 to 9 years				
1	73.6(32)	65.8(28)	59.3(16)	59.2(33)
2	49.6(21)	43.8(32)	51.9(4)	44.9(67)
3	33.3(21)	35.5(39)	35.2(7)	32.1(58)
4	30.9(4)	33.0(53)	35.6(5)	29.1(44)
5	24.5(2)	27.1(79)	—	26.4(60)
6	—	—	—	20.5(56)

[a] Sample sizes in parentheses.

The effect associated with parental employment appears to be much more prominent in the most contaminated study areas nearest to the smelter. This may be the effect of an intervening socioeconomic variable: the lowest paid workers, employed in the highest exposure areas within the industry, might be expected to live in the most undesirable locations, which are closest to the smelter.

The importance of the infiltration by lead dusts into clothing, particularly the undergarments, of lead workers has been demonstrated in a number of studies of the effects of smelters.[133] It was noted in the United Kingdom that elevated blood lead levels were found in the wives and children of workers even when they resided some considerable distance from the facility. It was most prominent in the families of workers who themselves had elevated blood lead levels. Quantities of lead dust were found in workers' cars and homes. It apparently is not sufficient for a factory merely to provide outer protective clothing and shower facilities for lead workers. In another study in Bristol, from 650 to 1400 ppm of lead was found in the undergarments of workers as compared with 3 to 13 ppm in undergarments of control subjects. Lead dust will remain on the clothing even after laundering: up to 500 mg of lead has been found to remain on an overall garment after washing.[134]

Baker et al.[135] found blood lead levels >30 μg/dl in 38 of 91 children whose fathers were employed at a secondary lead smelter in Memphis, Tenn. Housedust, the only source of lead in the homes of these children, contained a mean of 2687 μg/g compared with 404 μg/g in the homes of a group of matched controls. Mean blood lead levels in the workers' children were significantly higher than those for controls and were closely correlated with the lead content of household dust. In homes with lead in dust < 1000 μg/g, 18 children had a mean blood lead level of 21.8 ± 7.8 μg/dl, whereas in homes where lead in dust was >7000 μg/g, 6 children had a mean blood lead level of 78.3 ± 34.0 μg/dl.

Landrigan et al.[62] also reported a positive history of pica for 192 of the 919 children studied in Idaho. This history was obtained by physician and nurse interviews of parents. Pica was most common among 2-year-old children and only 13 percent of those with pica were above age 6. Higher blood lead levels were observed in children with pica than in those without pica. Table 12-39 shows the mean blood lead levels in children as they were affected by pica, occupation of the father, and distance of residence from the smelter. It is interesting that, among the

TABLE 12-39. GEOMETRIC MEAN BLOOD LEAD LEVELS FOR CHILDREN BASED ON REPORTED OCCUPATION OF FATHER, HISTORY OF PICA, AND DISTANCE OF RESIDENCE FROM SMELTER[62]

		Lead smelter worker		Lead/zinc mine worker		Zinc smelter worker		Other occupations	
Area	Distance from smelter, km	Pica	No pica	Pica	No pica	Pica	No pica	Pica	No pica
1	1.6	78.7	74.2	75.3	63.9	69.7	59.1	70.8	59.9
2	1.6 to 4.0	50.2	52.2	57.1	46.9	62.7	50.3	37.2	46.3
3	4.0 to 10.0	33.5	33.3	36.7	33.5	36.0	39.6	33.3	32.6
4	10.0 to 24.0	—	30.3	38.0	32.5	40.9	36.9	—	39.4
5	24.0 to 32.0	—	24.5	31.8	27.4	—	—	28.0	26.4
6	75.	—	—	—	—	—	—	17.3	21.4

populations living nearest to the smelter, environmental exposure appears to be sufficient at times to more than overshadow the effects of pica, but this finding may also be caused by inadequacies inherent in collecting data on pica.

These data indicate that in a heavily contaminated area, blood lead levels in children may be significantly increased by the intentional ingestion of nonfood materials having a high lead content.

Data on the parents' occupations are, however, more reliable. It must be remembered also that the study areas were not homogeneous socioeconomically. In addition, the type of work an individual does in an industry is probably much more important than simply being employed in a particular industry. The presence in the home of an industrial employee exposed occupationally to lead may produce increases in the blood lead levels ranging from 10 to 30 percent.

12.3.6 **Miscellaneous Sources of Lead**

Although no studies are available, it is conceivable that destruction of lead-containing plastics (to recover copper), which has caused cattle poisoning, also could become a source of lead for humans. A more general problem is waste disposal, because lead-containing materials may be incinerated and may thus contribute to increased air lead levels. This source of lead has not been studied in detail.

The consumption of illicitly distilled liquor has been shown to produce clinical cases of lead poisoning. Domestic and imported earthenware with improperly fired glazes have also been related to clinical lead poisoning. This source becomes important when foods or beverages high in acid are stored in containers made from these materials because the acid releases lead from the walls of the containers.

Particular cosmetics popular among some Oriental and Indian ethnic groups contain high percentages of lead that sometimes are absorbed by users in quantities sufficient to be toxic.

12.4 SUMMARY

Blood lead levels in homogeneous human populations have almost invariably been found to be lognormal. A number of such data sets were examined and they displayed a geometric standard deviation (GSD) ranging from 1.3 to 1.5.

From the lognormal distribution, given a mean blood lead level and an estimated geometric standard deviation, it is possible to predict the percentages of a population whose blood lead levels exceed a specified value. It is also possible to estimate the likely increase in mean blood lead levels for a population exposed to specific increases in environmental lead. Coupling these two procedures provides a method by which standards may be chosen to protect the health of the population.

Blood lead levels have been found to exhibit considerable geographic variability. Generally they are lowest in rural settings, higher in suburban areas, and highest in inner-city areas. These values follow the presumed lead exposure gradient. Blood lead values were also found to vary by age, sex, and race, although in a somewhat more complex fashion. Generally, young children have the highest levels, with little difference between sexes. In older segments of the population, after eliminating occupational exposure in lead workers, males have a higher blood lead than females. The published data comparing the blood lead levels of various racial and ethnic groups of the population suggest that blacks have higher blood lead levels than whites, with Puerto Ricans sometimes at an intermediate level.

Results of the numerous studies of environmental exposures of man have indicated strongly that man does indeed take up lead from each source to which he is exposed. Equally important, these studies have shown that the blood lead level is the summation of the absorption from each of these sources.

Data for the two most widespread environmental sources other than food permit summary statements concerning their quantitative relationship with blood lead levels: ratios between blood lead levels and air lead exposures were shown to range generally from 1:1 to 2:1. These were not, however, constant over the range of air lead concentrations encountered. There are suggestive data indicating that the ratios for children are in the upper end of the range and may even be slightly above it. There is also some slight suggestion that the ratios for males are higher than those for females.

For soil lead exposures, a consistent association with blood lead levels has been established. Children exposed to higher soil and housedust lead concentrations have been shown to have elevated concentrations of lead on their hands, but an association of elevated blood lead levels with elevated hand lead levels has not yet been established. Quantitatively, blood lead levels have been shown to increase 3 to 6 percent when the soil or dust lead content is doubled.

Significant water lead exposures in this country have occurred only in places using leaded pipes coupled with a soft water supply. Such exposures have been shown to be associated with significant elevations of blood lead. They have also been linked to cases of mental retardation.

Exposure to leaded paint still comprises a very serious problem for American children in urban settings. Although new regulations governing the lead content of paint should alleviate the problem in new housing, the poorly enforced regulation and lack of regulation of the past have left a heavy burden of lead exposures from paint. Most of the studies on lead poisoning in children have assumed an association with leaded paint, but very rarely have these studies measured the amount of exposure. There is, nevertheless, strong suggestive evidence that the contribution from this source can be very significant.

Lead exposure via food is thought to be the source of a significant portion of blood lead. Direct quantitative equations describing the relationship of blood to food lead levels have not been published, but studies described in Chapter 10 do address this relationship.

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13. EVALUATION OF HUMAN HEALTH RISKS FROM EXPOSURE TO LEAD AND ITS COMPOUNDS

13.1 INTRODUCTION

The preceding chapters of this document have described lead production, the economics of lead utilization, the dispersion of lead in the environment —particularly in air, dust, and soil —and, finally, have reviewed the effects of lead on the health of man. Although attempting to relate these various issues to one another, this chapter specifically will attempt to assess and to quantitate the health effects that arise from exposure of man to lead in the environment and, more precisely, from exposure to lead in air. Six central questions to be addressed are as follows:

1. What are the sources of lead in the environment? (Sections 13.2 and 13.3)
2. What are the routes and mechanisms by which lead from these sources enters the body? (Sections 13.2 and 13.3)
3. What part do averaging times for these exposures play? (Section 13.4)
4. How does the body respond to the entrance of lead? (Section 13.5)
5. Are there groups within populations which are particularly vulnerable to lead? (Section 13.6)
6. What is the magnitude of the risk exposures in terms of the number of persons exposed in various subgroups of populations? (Section 13.7)

Each of the above questions is addressed separately as a subsection of this chapter, and the relevant section is noted beside each question.

Now that the questions to be addressed in this treatment of risk assessment have been outlined, it is necessary to define the terms which will be employed. These include:

1. *Dose* is the amount or concentration of a chemical that is presented over time to an organism, organ, cell, or subcellular component. Ideally, dose should be defined as the amount or concentration of the chemical at a specific intracellular site of effect.
2. *External dose* is the amount of the contaminant in the external environment (air, water, food, etc.) to which humans are exposed.
3. *Effective dose* or *internal dose* is the amount of the contaminant absorbed by the body.
4. *Effect* is a biologic change which results from exposure to a chemical.
5. *Dose-effect relationship* is a quantitative relationship between the dose and the specific effect that is established after gradations in the severity of an effect have been measured.
6. *Critical effect* is the first adverse functional change, reversible or irreversible, to be caused by exposure to a particular chemical.
7. *Subcritical effect* is a change that is demonstrable by biochemical or other test, but which does not appear to impair function; some such changes may be adaptive in nature.
8. *Critical dose* or *critical concentration* is the level of a chemical at which the critical effect appears.
9. *Critical organ* is the organ which manifests the critical effect; it need not be the organ with the highest concentration of the chemical nor that which ultimately suffers the most serious injury.

Dose-effect relationships will vary among the members of a population. Response is the proportion of the population that manifests a particular effect at a particular dose level.[1] This is a more restrictive definition of response than that used in bioassay as described by Finney.[2] The relationship between dose and the proportion responding is the dose-response relation, which will most commonly be expressed by a sigmoid-shaped curve.

13.2 SOURCES, ROUTES, AND MECHANISMS OF ENTRY

13.2.1 Sources

Of the estimated 161,225 metric tons of lead emitted into the atmosphere in 1975, the combustion of gasoline additives and waste oil accounted for 95 percent of total inventoried emissions. Each of the remaining emission sources accounts for only a small part of the total quantity of lead, but has the potential of creating localized situations of high air lead concentrations, e.g., primary lead smelters.

Once lead is introduced into the air it undergoes a variety of processes including dry deposition, precipitation, and resuspension. These processes result in a variable proportion of lead being retained in the air and then being distributed over a wide area. Other portions are deposited on land, in dust, and on water, resulting in increased lead concentrations in each.

Other uses of lead result in additional human exposure. The addition of lead to paint makes lead directly available by ingestion of paint chips and paint-saturated plaster. In addition it becomes indirectly available through dust contaminated with lead freed by the weathering process of paint. This primary source is currently under regulation, but a vast stock of housing painted with high-lead-content paint still exists.

Lead's malleability and ductility have resulted in the use of this metal in pipes for carrying drinking water. When such pipes are used in areas with soft water of low pH, a potential exists for heavy lead contamination of drinking water. It is difficult to estimate the overall magnitude of this danger, but there have been specific localized examples in the United States.

A final quantitatively significant source of lead is the human diet. Lead present in foodstuffs is the sum of the amount present in the raw foodstock and of lead introduced via processing and packaging. Canned products such as vegetables and milk have been shown to contain higher quantities of lead than the same products packaged differently. This is due, in part, to the presence of lead solder in the seams of cans. Baby foods have also been shown to have higher lead contents because of the preservatives used. The origin of lead in raw food stocks is still a matter of some controversy, although part of it is likely to be the consequence of man's activities which result in making lead available for uptake by animals and plants. Such redistribution and subsequent uptake of lead by plants is well illustrated by fivefold increases in the amount of lead present in tree rings over a 50-year period.

It is important to realize that human exposure and intake are not limited to the primary sources of lead in the environment but, rather, to the sum of primary, secondary, and tertiary sources. Table 13-1 displays these sources.

TABLE 13-1. SOURCES OF LEAD FOR HUMAN EXPOSURES

Primary exposure source	Secondary exposure source	Tertiary exposure source
Air	Dust and soil	Food Runoff water
	Water	Air[a]
Paint	Dust and soil	Runoff water Air[a]
Water from leaded pipes		
Food		

[a] Reentrainment

13.2.2 Routes and Mechanisms of Entry

Chapter 10 presents data on the entry of lead into the human body. Two routes of entry are of principal importance, inhalation and ingestion. Intake of airborne lead is governed by the physical and chemical state of inhaled lead, particle size retention in the lung, and absorption from the lung into the red blood cells.

The second major route of entry is ingestion, both of food and of nonfood material. Uptake is controlled by the nutrient balance of the food ingested, particularly that of iron, by the physical nature of the lead-bearing material ingested, and by the chemical composition of the substance. Here, too, the lead is absorbed by circulating red blood cells.

The total internal dose of lead which confronts the organ systems of the body is the sum of the lead intake by both routes of entry: inhalation and ingestion. Thus the total internal dose represents the summation of all external sources to which the body is exposed. Some of these exposures may be of different relative significance in diverse population groups due to variances in metabolism or behavior among different segments of the population.

13.3 EVIDENCE OF INCREASED BLOOD LEAD LEVELS IN HUMANS EXPOSED TO ENVIRONMENTAL LEAD

13.3.1 Relationships Between Blood Lead Levels and Single-Source Exposures

Research has been conducted on all six major exposure sources — air, dust, soil, water, paint, and food. Chapter 12 provided the detailed description, evaluation, and findings of those studies. Not all sources have been studied with the same intensity, and food has been studied least. In addition, food as a tertiary exposure source is difficult to evaluate. Lead content in food due to packaging and processing has been studied more thoroughly than contribution from that lead present at the point of origin.

Single-source studies of air have included both epidemiological and clinical investigations. Clinical data uniformly demonstrate the actual uptake of airborne lead into blood, and epidemiologic data also generally support such a relationship.

Studies concerned with dust and soil lead exposures will be considered together since in many studies the investigators did not attempt to deal with these sources separately. Considerable evidence exists that these exposures can be significant determinants of blood lead levels. Furthermore, investigations of children exposed to lead-contaminated dust have demonstrated more lead on the children's hands, thus documenting a plausible route of entry which is due to normal oral behavior in young children. It may be worth reiterating here that the dose of lead ingested from dust and soil appears to be additive to that inhaled from air.

The popular assumption that lead-based paint is the single causative agent of elevated blood lead levels in children has resulted in limiting the definition of high-risk children to those residing in older housing. As a result, lead screening programs have been established with the sole purpose of identifying children with elevated lead levels among those living in old housing. Abatement efforts have frequently been unable to find lead paint sources for children with high blood levels found by such screening programs. The possible contributory role of airborne lead to the lead burden of urban children has until recently received little attention.

Finally, studies from Glasgow and Boston have shown elevated blood lead levels in conjunction with elevated levels of lead in the drinking water.

Secondary effects of occupational exposure have been examined in children whose parents work in lead industries. It has been found that parents carry home lead-contaminated dust. Significant relationships between house dust levels and blood lead levels have invariably been established in these studies.

13.3.2 **Multiple-Source Exposures**

Studies measuring the quantity of lead in multiple sources, around primary lead smelters or in urban settings, have consistently demonstrated an additive relationship between blood lead levels and exposure to the several sources studied.

13.3.3 **Effect of Host Factors on Blood Lead Levels**

Host characteristics that mediate the relationship between exposure to lead and blood lead level have been examined in several studies. In particular, age has been shown to be a significant factor in determining blood lead levels; this relationship is discussed below in more detail in the section (13.6) on populations at greatest risk.

Sex differences have been found to be age related. Particularly among preschool boys and girls, virtually no difference has been established. In the adult population, however, males generally exhibit higher levels than females.

Data on the racial/ethnic factor are sparse. One study has reported that black children have higher lead levels than do white children. Although the significance of the racial/ethnic factor cannot be established at this time, it seems reasonable to assume that it is the socioeconomic rather than the genetic dimension of this variable that may prove to be relevant.

Socioeconomic variables such as income and education have not been examined adequately as independent factors. Associated characteristics such as residence in old housing, or proximity to high-density traffic arteries or to stationary sources such as smelters, have been shown to be directly relevant.

In epidemiological studies the health status as a variable has not been examined. Conditions such as iron deficiency anemia, other states of malnutrition, sickle cell anemia, and lactose intolerance as host factors in lead intake and determinants of physiological and pathological changes have only recently come under study. No findings are available as yet.

13.3.4 **Summary of the Quantitative Relationship**

Statistical evaluation of the data collected from population and clinical studies has been presented in the previous chapter. There it was noted that the weight of the evidence indicates that blood lead levels follow a lognormal distribution in exposed populations with a geometric standard deviation of 1.3 to 1.5. It was also seen that the lognormal distribution has properties that make it amenable to use in the standard-setting process, since it permits an estimate of the proportion of the population whose blood lead levels exceed any specified level.

Detailed examination of the clinical and epidemiological studies relating air lead levels to blood lead levels is presented in Chapter 12. Evidence indicates that a positive relationship exists between blood and air lead levels, although the exact functional relationship has not yet been clarified. Available data indicate that in the range of air lead exposures generally encountered by the population, the ratio of the increase in blood lead per unit of air lead is from 1 to 2. It appears that the ratio for children is in the upper end of the range and that ratios for males may be higher than those for females.

Quantitative relationships can also be established between blood lead levels and exposure to lead in soil. There is general agreement that blood lead levels begin to increase at soil lead levels of from 500 to 1000 ppm. Mean percent increases in blood lead levels, given a twofold increase in soil lead levels, ranged from 3 to 6. This is a remarkable consistency, given the divergence of the populations studied.

13.4 AVERAGING-TIME CONSIDERATIONS

One of the major areas of concern in dealing with quantitation of the relationship between a health effect and an external dose of some environmental pollutant is the determination of how long an exposure must occur before there is an effect.

Evidence presented in Chapter 12 indicates that a 5 μg/dl increase in blood lead can result from an air lead exposure of 3.2 μg/m^3 for a period of 7 weeks. Furthermore, FEP levels have been shown to increase within 2 weeks of an increase of blood lead levels. Therefore, an air lead exposure of 3.2 μg/m^3 lasting about 1 to 2 months can definitely increase the blood lead level.

13.5 BIOLOGICAL AND ADVERSE HEALTH EFFECTS OF LEAD IN MAN

Lead does not presently have associated with it any biological effect in man which can be considered beneficial; therefore, any consideration of the health effects of lead in man must be done from a point of view that acknowledges the absence of any health benefit/health cost ratio.

An additional and extremely important aspect of lead's effect on health impairment that must be considered in risk assessment is the question of whether these effects are reversible once present.

Physiological damage to central nervous system tissue is presently widely accepted as being irreversible; thus prevention of lead exposure is most urgent when one considers severe neurological effects. Irreversibility is also accepted in the case of renal tissue damage resulting from chronic lead exposure, particularly in cases where these effects are manifested morphologically.

We speak of physiological irreversibility in the cases of neurological or renal tissues, but the concept of irreversibility of an effect being likely or assured by nonbiological factors such as continuing, long-term exposure to airborne lead must also be considered. Hematological effects are of relevance here. Although a number of these hematological effects may be biochemically reversible, if the probability of the person being removed from the exposure setting inducing these effects is slight or nonexistent, for whatever reason, then *defacto* irreversibility exists.

This section summarizes the biological effects of lead on man with particular reference to significance of these effects for human health. Much of the attention in this section will be directed to those biological effects which may collectively be termed "subclinical." By definition, subclinical effects are disruptions in function, which may be demonstrated by special testing but not by the classic techniques of physical examination; using the term "subclinical" in no way implies that those effects are without consequences to human health.

13.5.1 Assessment of Hematological Effects of Lead

A multiplicity of effects of lead on the hematopoietic system exists. These effects were discussed in detail in Chapter 11, Section 3, and are briefly summarized here.

13.5.1.1 ANEMIA

Anemia is a classic manifestation of clinical lead intoxication, often occurring prior to neurological and other system impairment. The mechanism of anemia in lead exposure apparently involves both decreased production of hemoglobin and enhanced destruction of erythrocytes. Reports on children indicate that statistically significant decreases in hemoglobin levels begin to appear at a blood lead level of 40 μg/dl or somewhat below. In adults a significant decrease in hemoglobin level appears to become evident at a blood lead level of 50 μg/dl.

13.5.1.2 LEAD EFFECTS ON HEME SYNTHESIS

A large number of studies have been done on the effects of lead on heme synthesis in humans. Lead interferes with heme synthesis at several points along the heme-biosynthetic pathway. The two most important points of interference are: (1) the condensation of two units of δ-aminolevulinic acid dehydratase to form porphobilinogen and (2) the insertion of iron into protoporphyrin IX which is catalyzed by the enzyme ferrochelatase.

13.5.1.3 EFFECT OF LEAD ON δ-AMINOLEVULINATE DEHYDRATASE (δ-ALAD) AND δ-AMINOLEVULINIC ACID (δ-ALA) EXCRETION

A number of studies have shown the high sensitivity of δ-ALAD to lead and the negative correlation between blood lead and the logarithm of δ-ALAD activity. These studies are described in Section 11.3. It appears that this relationship holds true for industrial workers, the general population, and children.

The dose-response relationship between blood lead and the logarithm of ALAD activity appears to be linear coefficient of correlation (r) = 0.84. ALAD inhibition is first noted at whole blood levels of 10 to 20 μg/dl (Chapter 11). This high degree of sensitivity makes application and interpretation of the test difficult. ALAD inhibition is virtually complete at blood lead levels of 70 to 90 μg/dl.

Data summarized by Hernberg[3] suggest that heme biosynthesis is not decreased by ALAD inhibition until activity of the enzyme has fallen to less than 20 to 30 percent of normal. In addition to its effect on red blood cell ALAD, lead appears to inhibit ALAD activity in liver. It has also been suggested that in young children lead may inhibit activity of ALAD in brain.

13.5.1.4 EFFECT OF LEAD ON IRON INSERTION INTO PROTOPORPHYRIN

Accumulation of protoporphyrin in erythrocytes in lead exposure is the result of lead-induced inhibition of the intramitochondrial enzyme, ferrochelatase. The inhibitory effect of lead on ferrochelatase may either be direct or may be mediated by a disruption in the function of mitochondrial membranes.

The effect of lead on the formation of heme is not limited to the hematopoietic system. Experimental animal studies have shown a lead effect on the heme-requiring protein, cytochrome P-450, an integral part of the hepatic mixed-function oxidase (Chapter 11), the systemic function of which is detoxification of exogenous substances. Heme synthesis inhibition also takes place in neural tissue.

The elevation of free erythrocyte protoporphyrin (FEP) has been shown by a large number of studies to be exponentially correlated with blood lead level in children and adults.

Present information shows that at relatively fixed blood lead values children and probably women have higher protoporphyrin levels in their blood than adult males. The exact reason for this is not known, but it may be of endocrinological origin.

Elevation in protoporphyrin is considered not only to be a biological indicator of impaired mitochondrial function of erythroid tissue but also an indicator of accumulation of substrate for the enzyme ferrochelatase. It therefore has the same pathophysiological meaning as increased urinary δ-ALA (*vide supra*). For these reasons accumulation of protoporphyrin has been taken to indicate physiological impairment in humans, and this clinical concensus is expressed in the 1975 Statement of the Center for Disease Control (CDC), USPHS. The criterion used by CDC to indicate an effect of lead on heme function is an FEP level of 60 μg/dl in the presence of a blood lead level above 30 μg/dl whole blood.

More recent information relating to threshold of lead effects indicates that FEP levels begin to increase at a blood lead value of 15 to 20 μg Pb/dl blood in children and women and, at a somewhat higher value, 20 to 25 μg Pb/dl blood, in adult men.

13.5.1.5 OTHER EFFECTS ON HEME SYNTHESIS

There are other abnormalities of heme synthesis that are a result of lead exposure. For example, it is well known that an increased urinary coproporphyrin level is found in lead poisoned children and lead workers. It is not known whether this effect results from specific enzyme inhibition, from upstream accumulation of substrate secondary to the inhibition of iron insertion into protoporphyrin, or from a disturbance of coproporphyrin transport through the mitochondrial membrane.

An increased activity of δ-ALA synthetase is seen in lead intoxication, but this change probably arises as a negative feedback control to δ-ALA response to inhibition upstream in the heme-biosynthetic pathway. Few data exist to quantitate the health significance of this effect.

13.5.1.6 EFFECTS OF LEAD ON GLOBIN SYNTHESES

Hemoglobin synthesis may also be impaired by the inhibition by lead of globin biosynthesis. Globin is the protein moiety of hemoglobin. One recent study shows an effect on globin synthesis *in vitro* on human reticulocytes at lead concentrations corresponding to a blood lead level of 20 μg/dl.

13.5.2 Assessment of Neurobehavioral Effects of Lead

As reviewed in Chapter 11, an extensive literature documents the adverse effects of lead on the central and peripheral nervous systems of many human and nonhuman mammalian species. Only limited dose-response data exist that might allow external lead exposure parameters to be linked directly to the occurrence of particular neurobehavioral effects. In contrast, more data exist relating blood lead levels to neurobehavioral deficits; major emphasis here is therefore focused on the concise summarization of relationships between human blood lead levels and neurobehavioral effects.

13.5.2.1 CENTRAL NERVOUS SYSTEM EFFECTS

Among the most profoundly deleterious effects of lead poisoning are those associated with severe CNS damage that occur at toxic high exposure levels. The acute overt manifestations of neural damage at high lead exposure levels include such symptoms as irritability, stupor, convulsions, and/or coma, which characterize the well-known encephalopathy syndrome. Such symptoms at times occur abruptly during the course of much milder symptomatology or even in apparently asymptomatic lead poisoned individuals and may progress to death within 48 hr.

Even in the absence of death or prolonged unconsciousness, it is now widely accepted that irreversible neural damage typically occurs as one of the sequelae of nonfatal lead encephalopathy episodes. Such permanent neural damage is reflected by signs of continuing CNS impairment ranging from subtle neurobehavioral deficits to severe mental retardation or continuing mental incompetence. What is not yet universally agreed upon, however, are the lead levels sufficient to produce lead encephalopathy and its sequelae.

In regard to the issue of threshold levels for lead encephalopathy, blood lead levels of 120 μg/dl or more are currently widely accepted as necessary to produce encephalopathy symptoms in adults. The published evidence bearing on this point, however, is very limited. Included among such evidence are a few scattered reports suggesting that acute encephalopathy or death may occur in adults at blood lead levels under 100 μg/dl (from 80 to 100 μg/dl), but the rarity of such cases and ambiguities in the reported data render it difficult to accept those reports as evidence for encephalopathy in adults at blood lead levels below 120 μg/dl.

Much better evidence exists for the occurrence of lead encephalopathy in children at blood lead levels below 120 μg/dl or even 100 μg/dl. That is, it is well documented that such symptoms occur for some children beginning at the 100 μg/dl level; also, several scattered reports suggest that somewhat lower threshold levels may obtain, i.e., in the 80 to 100 μg/dl range, although such reports must be viewed with caution as in the case for analogous results for adults.

As indicated earlier, the issue of whether apparently asymptomatic children experience subtle neurobehavioral deficits at low-to-moderate blood lead levels in the 40 to 80 μg/dl range remains a subject of much controversy. A thorough, critical review of the relevant literature presented in Chapter 11, nevertheless, leads to the conclusion that blood lead levels of 50 to 60 μg/dl are likely sufficient to cause significant neurobehavioral impairments for at least some apparently asymptomatic children. The impairments consist mainly of cognitive or sensory-motor integration deficits, but do not appear to include the occurrence of hyperactivity; that latter effect seems to be much better established as one of the neurological sequelae following encephalopathy at higher lead levels.

13.5.2.2 PERIPHERAL NEUROPATHY EFFECTS

In addition to the above CNS effects, peripheral nervous system damage also results from exposures to lead. Such effects have been best documented as occurring after long, chronic, high-level exposures in adults exhibiting other symptoms of lead intoxication. Recent studies of apparently asymptomatic adults, usually occupationally exposed to lead, however, present reasonably strong evidence for peripheral neuropathy at more moderate lead exposure levels, i.e., at blood lead levels in the range of 50 to 70 μg/dl. Peripheral neuropathy effects are typically associated with adult exposures, having been reported much less frequently for children. A few reports of lead-induced peripheral neuropathies in children, however, contain evidence for the occurrence, in some rare instances, at blood lead levels as low as 50 to 60 μg/dl.

13.5.2.3 RESULTS OF ANIMAL STUDIES AS SUPPORTIVE EVIDENCE

Review of the literature on the neurobehavioral effects of lead in animals provides evidence supportive of the above conclusions from human studies. That is, there appears to be a differential sensitivity of newborn or young animals of many species to the neurobehavioral effects of lead. This applies both to the induction of lead encephalopathy at high exposure levels and more subtle neurobehavioral deficits at lower, more moderate exposure levels. In regard to specific types of subtle neurobehavioral effects, hyperactivity appears to occur mainly at blood lead levels in excess of 70 to 80 μg/dl and, therefore, probably most closely parallels the post encephalopathic hyperactivity well demonstrated as one of the sequelae of lead encephalopathy in humans. Other behavioral changes, interpreted as indicative of cognitive impairments resulting from CNS effects, appear to occur in animals at blood lead levels below those associated with acute encephalopathic effects, i.e., in the 30 to 80 μg/dl blood lead level range. This parallels rather closely the effects observed for humans, especially children, except that cognitive deficits have not been very well documented in the children at levels below 50 to 60 μg/dl. The external lead exposures yielding the above results for animals, however, typically appear to be much higher than those producing comparable effects in humans; the comparability of animal studies and human studies is therefore often questioned. If one focuses on the resulting blood lead levels achieved, regardless of associated external dose, however, the results of the animal studies parallel those of the human studies remarkably well.

In discussing the neurobehavioral effects of lead, above in the present section and in Chapter 11, a distinction has repeatedly been made between threshold levels yielding severe symptoms of lead encephalopathy seen at high exposure levels and more subtle neurobehavioral deficits observed at lower exposure levels. This approach may inappropriately convey an impression of such effects occurring in a discrete, step-like fashion as particular threshold blood lead levels are reached. It is important to note that this may occur insofar as shifting from apparent no-effect levels to levels at which fairly well substantiated neurobehavioral effects have been found to occur, i.e., around 50 to 60 μg/dl; beyond that point, however, further increases in relative levels of neural damage, as indicated by increasingly severe neurological or behavioral deficits, occur in a more or less smoothly ascending fashion in relation to increasing blood lead levels. These relationships are presented later in an approximate manner in Table 13-2. Due to differences in individual susceptibility, it should be emphasized that the upper end of the range of blood lead levels at which subtle neurobehavioral effects have been reported to occur for some individuals merges or overlaps substantially with the lower end of the range at which much more severe encephalopathic symptoms have been observed, and that the shift from subtle to severe neural symptoms may be quite abrupt.

13.5.3 **Effects of Lead on Reproduction and Development**

Although the effects of lead exposure in humans have usually been associated with the hematopoietic, neural, and renal systems, concern needs to be equally directed to the entire area of reproduction and development, with special emphasis on the vulnerability of pregnant women or, more accurately, the vulnerability of the fetus.

Attention in this area is focused on two aspects of reproduction: (1) the gametotoxic effects of lead, i.e., lead effects on spermatogenesis and ovarian function, and (2) postconception events through delivery.

13.5.3.1 HUMAN GAMETOTOXICITY

Some data involving effects of lead exposure on the fertility of males exist, and these have been observed at blood lead levels of 50 to 80 μg/dl under conditions of occupational exposure. With regard to women, one study on lead effects (see Reproduction and Development section, Chapter 11) raises the possibility that the ovarian cycle may be disturbed in the age range of 20 to 25 years with air lead levels around 7 $\mu g/m^3$.

13.5.3.2 POSTCONCEPTION LEAD EFFECTS

Both early literature and more current studies conclusively show that lead crosses the placental barrier. Such fetal exposure therefore commences at about the end of the first trimester (12 weeks) and continues throughout fetal development. As has already been pointed out, the distribution of lead within the fetus at different stages of development is probably more important than the total amount present at birth.

Tissue analysis also demonstrates that, in Americans from newborns through persons aged 19 years, brain lead levels appear to be most elevated at birth and then diminish with development.

A number of studies show passage of lead through the placental barrier by comparing cord blood lead and maternal blood lead levels. These studies further serve to shed some light on the effect of various factors in infant blood lead values.

In a group of cord blood/maternal blood matchings, infant blood levels were highly correlated with those of their mothers. A second study showed that blood values for infants whose mothers were urban residents were significantly higher than those of rural infants.

A study done in a lead-belt area of the United States raises the possibility that lead may affect the course of normal delivery of children since there were more incidents of preterm delivery and premature membrane rupture in pregnant women in this region compared to a group from a relatively unexposed area.

13.5.4 **Other Health Effects**

13.5.4.1 RENAL EFFECTS

Nephropathy is a condition usually considered in its chronic form and that can best be related to prolonged exposure to lead with a corresponding blood lead level of about 70 μg/dl. Because chronic lead nephropathy results only after prolonged or repeated exposures, it is impossible to recapitulate accurately the exposure history; therefore, determination of an exposure threshold for this condition is impossible.

13.5.4.2 EFFECTS OF LEAD ON THE ENDOCRINOLOGICAL, HEPATIC, CARDIOVASCULAR, AND IMMUNOLOGICAL SYSTEMS

Although some studies have been done in reference to each of the systems in this subsection, there exists too little quantitative information relating blood lead levels to the endocrinological, hepatic, and cardiovascular systems.

13.5.5 **Does-Effect/Response Relationships**

In any discussion of the risk assessment directed toward a particular agent, such as lead, two questions arise:

1. What are the lowest levels of the internal dose (blood lead level) that give rise to any biological effect?
2. What dose-response relationships are obtained that define a proportion of a population manifesting a given biological effect at a particular internal dose?

Information summarized in the preceding section dealt with relationships between blood lead levels and various biological effects of lead. Many of the data discussed above concerned threshold levels at which health effects of lead are first observed in different population groups. Table 13-2 summarizes the threshold levels at which various specific hematological and neurobehavioral effects have been observed for particular subpopulations.

A number of investigators have attempted to quantitate more precisely lead's dose-response relationship, i.e., the proportion of a population exhibiting health effects at a given blood lead level. Due to the limited availability of data, most such attempts have been restricted to effects on the hematologic system, in particular the elevation of FEP, the inhibition of ALAD activity, and the excretion of ALA in the urine.

TABLE 13-2. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS

Lowest observed effect level	Effect	Population group
10	ALAD inhibition	Children and adults
15 - 20	Erythrocyte protoporphyrin elevation	Women and children
25 - 30	Erythrocyte protoporphyrin elevation	Adult males
40	Increased urinary ALA excretion	Children and adults
40	Anemia	Children
40	Coproporphyrin elevation	Adults and children
50	Anemia	Adults
50 - 60	Cognitive (CNS) deficits	Children
50 - 60	Peripheral neuropathies	Adults and children
80 - 100	Encephalopathic symptoms	Children
100 - 120	Encephalopathic symptoms	Adults

In regard to defining dose-response relationships for hematological effects, three different assessments of such relationships have been carried out[4-6] and published. For example, in the approach of Zielhuis,[4] dose-response relationships were developed for ALAD, ALA-U, and FEP as obtained for adults, male and female, and children. In Figure 13-1 are presented the dose-response data for children and adults for ALAD at inhibition levels of 40 and 70 percent. In Figure 13-2, a corresponding relationship for urinary ALA is given for adult males, and Figure 13-3 presents the corresponding data for FEP in adult males, adult females, and children.

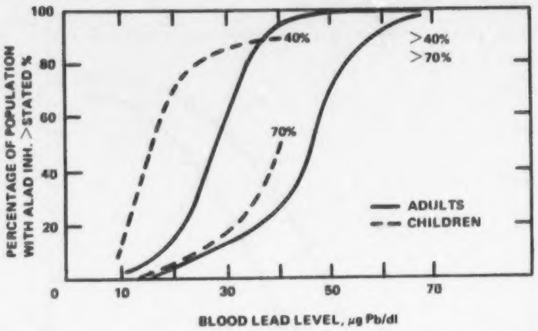

Figure 13-1. Dose-response curve for percent ALAD inhibition for adults and children as a function of blood lead level.[4]

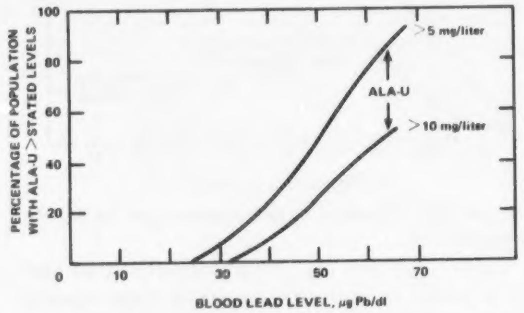

Figure 13-2. Dose-response curve for ALA in urine (ALA-U) as a function of blood lead level.[4]

As can be seen from Figure 13-1, there appears to be a marked difference at 40 percent inhibition of ALAD activity between children and adults, such a difference decreasing as one goes to 70 percent inhibition. For example, at 20 μg/dl blood lead, approximately 10 percent of adults show 40 percent enzyme inhibition, whereas the corresponding value for children is somewhat above 80 percent. It should also be noted that there is apparently a steep rise in the linear portion of these sigmoid relationships, e.g., 20 percent of adults show a 40 percent inhibition in ALAD at 20 μg/dl blood lead, whereas virtually all of the adult population shows 40 percent inhibition at 40 μg/dl. A similar steepness in the curve is seen in regard to children.

Figure 13-2 presents dose-response data for ALA in urine exceeding two discrete levels, >5 and >10 mg/liter, with increasing blood lead. It may be seen that the response in the linear portion of the curve is much less steep than for ALAD. For example, for approximately 5 percent of adults, the no-response level for ALA >5 mg/liter is about 30 μg/dl blood lead. At 60 μg/dl blood lead, the corresponding percentage of the population showing this response is in excess of 80 percent. The corresponding plot for ALA >10 mg/liter shows a less steep slope than the former case. At 60 μg/dl blood lead, the corresponding percentage of the adult population is approximately 40.

The composite dose-response plot presented in Figure 13-3 shows an increased response in FEP in adult females compared to adult males. Children show a greater response than adult males only up to blood lead levels of about 45 μg/dl. The data of Zielhuis are extracted from a number of reports. In Figure 13-4, interestingly, wherein are contained the

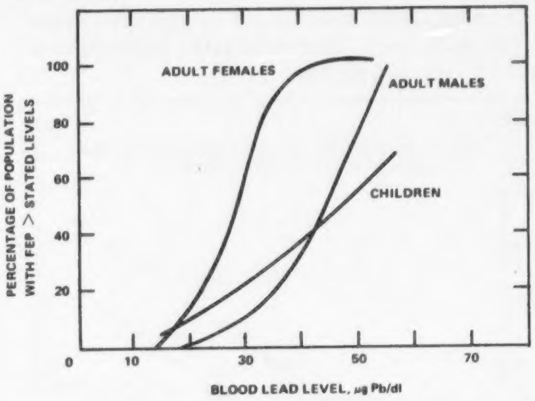

Figure 13-3. Dose-response curve for FEP as a function of blood lead level.[4]

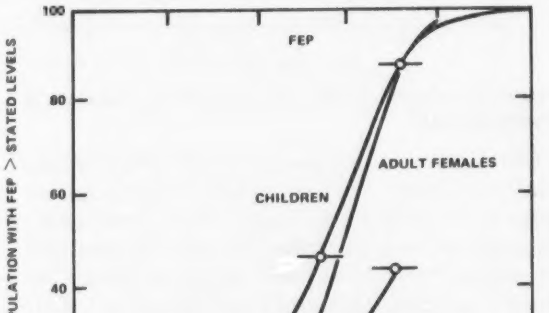

Figure 13-4. Dose-response curve for FEP as a function of blood lead level.[5]

dose-response data of Roels et al.[5] for FEP in adult males, adult females, and children, it appears that children show the most heightened response, followed by adult females, and the least response in adult males. The slope for the linear portion of the response curve is quite steep in the case of children; 20 percent of the children show elevated response (82 μg/dl rbc) at 20 μg/dl blood lead, whereas virtually all the children exceed this value at 35 μg/dl blood lead.

The dose-response data of Piomelli[6] are presented in Figure 13-5 and consist of composite plots for mean plus 1 standard deviation (33 μg/dl whole blood) and the mean plus 2 standard deviations (51 μg FEP/d1 whole blood). In the data presented in Figure 13-5, blood lead levels in excess of 28 μg/d1 whole blood were not used in the calculations. It appears from the above that there exists a threshold at about 15 μg/dl whole blood.

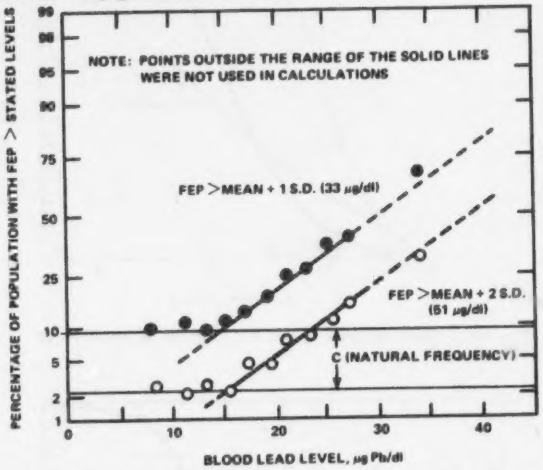

Figure 13-5. Dose-response curve for FEP as a function of blood lead level.[6]

EPA has carried out analyses of the data from the Azar et al. study[7] and calculated a dose-response curve for urinary ALA (Figure 13-6). These dose-response curves were plotted for two different cut-off points. These points were the mean values for blood lead levels less than 13 μg/100 g, plus 1 standard deviation and plus 2 standard deviations, respectively. From the mean plus 2 standard deviations curve, it is readily apparent that the linear portion of the curve is quite steep. At a blood lead level of 20 μg/dl, only 6 percent of the population exceed the mean plus 2 standard deviations value of the control population, whereas at a blood lead level of 50, 50 percent of the population exceeds that value. Furthermore, when one examines the figure at 40 μg/dl, the value at which ALA in urine is taken to suggest health impairment, the Azar et al. data show that about 30 percent of the population shows an elevation in this parameter.

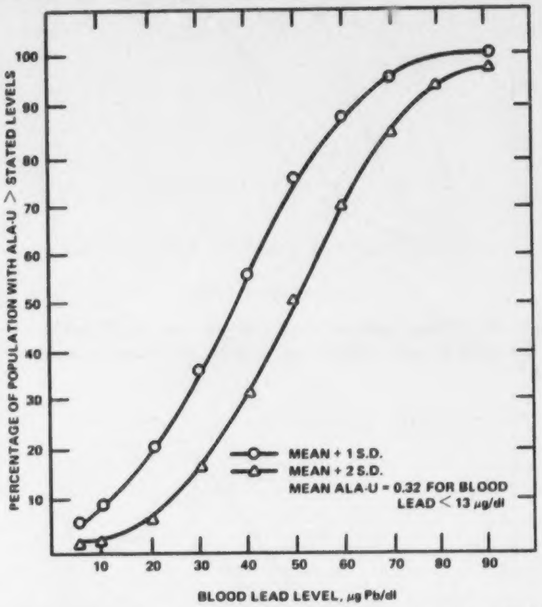

Figure 13-6. EPA calculated dose-response curve for ALA-U (from Azar et al.[7]).

In Table 13-3 are tabulated proportions of the study populations in the Zielhuis and Azar reports showing elevated urinary ALA versus blood lead level. The data for Zielhuis are as cited in Figure 13-2, the percentage of subjects with ALA-U greater than 5 mg/liter being used. The Azar data in Table 13-3 refer to the mean plus two standard deviations data set. For purposes of comparison of dose-response data for FEP, the studies of Zielhuis,[4] Roels,[5] and Piomelli[6] are tabulated in Table 13-4. As in the case for the table of ALA-U data, it should be kept in mind that differences exist in cut-off points for FEP response to lead in the various studies.

TABLE 13-3. ESTIMATED PERCENTAGE OF SUBJECTS WITH ALA-U EXCEEDING 5 mg/liter FOR VARIOUS BLOOD LEAD LEVELS

Blood lead levels, μg/dl	Zielhuis,[4] %	Azar et al.,[7] %
10	0	2
20	0	6
30	6	16
40	24	31
50	48	50
60	76	69
70	96	84

TABLE 13-4. ESTIMATED PERCENTAGE OF CHILDREN WITH EP EXCEEDING CUT-OFF POINTS FOR VARIOUS BLOOD LEAD LEVELS

Blood lead level, μg/dl	Zielhuis,[a] %	Roels et al.,[b] %	Piomelli,[c] %
10	0	3	9
20	6	27	11
30	22	73	48
40	37	100	80
50	49	---	---
60	---	---	---
70	---	---	---
80	---	---	---

[a] EP > EP of children with Pb-B < 20 μg/dl.

[b] EP > 82 μg/dl cells

[c] EP > EP of 33 μg/dl

13.6 POPULATIONS AT RISK

Population at risk is a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status. This high risk may result from either greater inherent susceptibility or from exposure situations peculiar to that group. What is meant by inherent susceptibility is a host characteristic or status that predisposes the host to a greater risk of heightened response to an external stimulus or agent.

In regard to lead, two such populations are definable. They are preschool age children, especially those living in urban settings, and pregnant women, the latter group owing mainly to the risk to the conceptus. Children are such a population for both of the reasons above, whereas pregnant women are at risk primarily due to the inherent susceptibility of the conceptus.

13.6.1 Children as a Population at Risk

Children are developing and growing organisms exhibiting certain differences from adults in terms of basic physiologic mechanisms, capability of coping with physiologic stress, and their relative metabolism of lead. Also, the behavior of children frequently places them in different relationship to sources of lead in the environment, thereby enhancing the opportunity for them to absorb lead. Furthermore, the occurrence of excessive exposure often is not realized until serious harm is done. Young children do not readily communicate a medical history of lead exposure, the early signs of such being common to so many other disease states that lead is frequently not recognized early as a possible etiological factor contributing to the manifestation of other symptoms.

13.6.1.1 INHERENT SUSCEPTIBILITY OF THE YOUNG

Discussion of the physiological vulnerability of the young must address two discrete areas. Not only should the basic physiological differences be considered that one would expect to predispose children to a heightened vulnerability to lead, but also the actual clinical evidence must be considered that shows such vulnerabilty does indeed exist.

In Chapter 10, Section 10.6 was devoted to the metabolic considerations in identifying susceptible subgroups. Factors discussed in that section included: (1) greater lead intake of infants on a per unit body weight basis, which is probably related to greater caloric and water requirement; (2) greater intake as well as net absorption (see GI section), greater net respiratory intake as well as greater net absorption and retention from the GI tract; (3) rapid growth rate may reduce the margin of safety against a variety of stresses including iron, calcium, and vitamin deficiency; (4) dietary habits of children are quite different from adults; normal hand-to-mouth activity probably results in the transfer of lead-contaminated dust and dirt via thumb sucking or in retrieval of dirt-contaminated foodstuffs; (5) the metabolic requirements for protein, calcium, and iron are so great relative to intake that a negative balance in these factors may exist; (6) in very young children metabolic pathways and factors such as the blood-brain barrier are known to be incompletely developed; and (7) partitioning of lead in the bones of children is different from that of adults. Only 60 to 65 percent of the lead body burden is in the bones of children, and this fraction may be more labile.

Hematologic and neurologic effects in children have been shown to have lower thresholds per unit of blood lead than in adults. In particular, the lowest observed effect levels for FEP and anemia are lower for children than adults. With reference to neurologic effects, the onset of encephalopathy and other injury to the nervous system appears to vary both regarding likely lower thresholds in children for some effects and in the typical pattern of neurologic effects presented, e.g., in encephalopathy or other CNS deficits being more common in children versus peripheral neuropathy being more often seen in adults. Not only are the effects more acute in children than in adults, but also the neurologic sequelae are usually much more severe in children.

Upon careful examination of the data, it should be noted that certain geographic or socioeconomic factors appear to emerge as important factors determining the differential susceptibility of some groups of children for lead-induced neurologic damage. That is, there seems to be distinct variation in effects or a lack thereof as reported for children in different studies depending upon the geographic areas from which the study populations were drawn. For example, the few credible reports of lead encephalopathy in children at blood lead levels less than 100 μg/dl all concern children from inner-city areas. Similarly, statistically significant effects or borderline effects indicative of more subtle neurobehavioral deficits in lead-exposed children at moderately elevated blood lead levels have been reported for groups of children drawn from inner-city populations of urban centers. In contrast, only a few statistically significant neurobehavioral effects have yet been reported for populations of children experiencing similar elevations in blood lead levels, but residing near primary smelter facilities in semirural areas.

One cannot determine with any certainty the specific factors that might contribute to the apparent differential sensitivity of inner-city children to the neurobehavioral effects of lead. Several possibilities, however, might be reasonably considered, including the following:

1. Parameters of lead exposure probably differed substantially for the populations under study; the smelter area children, for example, may have experienced much more gradual accumulations of lead during the course of long-term, low-level exposures versus probable repeated brief episodes of somewhat higher level exposures being superimposed on any long-term, low-level exposures for the inner-city children.
2. The exposures of the smelter children likely included significantly higher levels of other metallic species, e.g., zinc, that are known to reduce the pathological impact of lead on many organ systems.
3. Differences in nutritional status likely existed between the smelter and inner-city children, with the latter probably having a higher incidence of iron, calcium, and vitamin deficiency; or other differences in dietary content and habits might be invoked as an explanation.
4. Interactions between lead exposures and other factors associated with the stresses of urban versus nonurban living may also contribute to the apparent differential susceptibility of inner-city chilren.

13.6.1.2 EXPOSURE CONSIDERATIONS

Children's dietary habits as well as the diets themselves differ markedly from adults and, as a result, place children in a different relationship to several sources of lead. The dominance of canned milk and processed baby food in the diet of many young children is an important factor is assessing their exposure to lead since both those foodstuffs have been shown to contain higher amounts of lead than components of the adult diet. The importance of these lead sources is not their relationship to airborne lead directly but, rather, their role in providing a higher baseline lead burden to which the airborne contribution is added

Children ordinarily undergo a stage of development in which they exhibit mouthing behavior, for example, thumbsucking. At this time they are at risk of picking up lead-contaminated soil and dust on their hands and hence into their mouths where it can be absorbed. Scientific evidence documenting at least the first part of the chain is available.

There is, however, an abnormal extension of the mouthing behavior, called pica, which occurs in some children. Although diagnosis of this is difficult, children who exhibit this trait have been shown to purposefully eat nonfood items. Much of the lead-based paint problem is known to occur because children actually ingest chips of leaded paint.

13.6.2 **Pregnant Women and the Conceptus as a Population at Risk**

There are some rather inconclusive data indicating that women may in general be at somewhat higher risk to lead than men. However, pregnant women and their concepti as a subgroup are demonstrably at higher risk. It should be pointed out that, in fact, it really is not the pregnant woman *per se* who is at greatest risk but, rather, the unborn child she is carrying. Because of obstetric complications, however, the mother herself can also be at somewhat greater risk. This section will first describe the general evidence for all women and then the evidence that pertains to pregnant women exclusively.

Studies have demonstrated that women, like children, in general tend to show a heightened response of erythrocyte protoporphyrin levels upon exposure to lead. The exact reason for this heightened response is not known but may relate to endocrine differences between men and women. In particular, the levels of testosterone may play a role in this response.

As stated above, the primary reason pregnant women are a high-risk group is because of the fetus each is carrying. In addition, there is some suggestive evidence that lead exposures may affect maternal complications of delivery.

With reference to maternal complications at delivery, information in the literature suggests the incidence of preterm delivery and premature membrane rupture relates to maternal blood lead level. Further study of this relationship as well as studies relating to discrete health effects in the newborn are required.

Vulnerability of the developing fetus to lead exposure arising from transplacental transfer of mother's blood lead content was discussed in Section 11.6. This process starts at the end of the first trimester. Cord blood studies involving mother-infant pairs repeatedly have shown a correlation between maternal and fetal blood lead levels. Furthermore, the observed positive correlation of urinary ALA levels with blood lead levels in newborns indicates that some heme-biosynthetic derangement is apparent at birth and must therefore have commenced *in utero*.

Further suggestive evidence, cited in Chapter 11, has been advanced for prenatal lead exposures of fetuses possibly leading to later higher instances of postnatal mental retardation among the affected offspring. The available data are insufficient to state with any certainty that such effects occur or to determine with any precision what levels of lead exposure might be required prior to or during pregnancy in order to produce such effects.

13.7 DESCRIPTION OF U.S. POPULATION IN RELATION TO PROBABLE LEAD EXPOSURES

In this section estimates are provided of the number of individuals potentially at risk to lead exposures. Unfortunately the latest census data are only from 1970,[8] although some estimates are available from the National Center for Health Statistics for 1975.[9] This is unfortunate since some significant changes are thought to have occurred in the population structure since the 1970 census.

Because most lead exposures, excepting areas with primary lead smelters, occur in what the Bureau of the Census calls urban areas, an estimate of the potential risk of airborne lead exposure can be made from the total urban population of the United States. That this may be an acceptable first approximation can be gleaned by comparing the frequency distribution of air lead concentrations for urban and rural National Air Sampling Network stations in Chapter 7. This comparison readily shows a distinct difference in exposure between the two types of stations. Based on examination of the urban stations as well as of literature data on both air lead and soil and dust lead values, a strong case can be made to support the assumption that the area which the Bureau of the Census calls the central city of the urban areas is at even higher risk of lead exposure.

Therefore, in regard to exposures other than localized point stationary sources of lead, the population at risk is the urban one and, in particular, the central city residents. For the United States in 1970, these values were 149 and 64 million people, respectively[8] (Table 13-5). From the table it can readily be seen that a higher proportion of the nonwhite population lives in urban areas than whites (80.7 versus 72.4 percent) and is possibly subject to greater exposure to airborne lead. Furthermore, this disparity is even greater when one considers the central city population only, which may be subject to even higher levels of lead pollution from a multitude of sources.

TABLE 13-5. POPULATION AND PERCENT DISTRIBUTION, URBAN AND RURAL, BY RACE 1970 CENSUS[4]

Area	White, % (10^3)	Black and other, % (10^3)	Total, % (10^3)
Urban	128.773 (72.4)	20,552 (80.7)	149.325 (73.5)
Inside urbanized areas	100.952 (56.8)	17,495 (68.7)	118.447 (58.3)
Central cities	49.547 (27.9)	14,375 (56.5)	63.922 (31.5)
Urban fringes	51.405 (28.9)	3,120 (12.3)	54.525 (26.8)
Outside urbanized areas	27.822 (15.7)	3,057 (12.0)	30.878 (15.2)
Rural	48.976 (27.6)	4,911 (19.3)	53.887 (26.5)
Total, United States	177.773	25.463	203.212

From the previous discussion of populations at risk, however, two subgroups of this total population were defined as being at even higher risk — children, especially those under 5, and pregnant

TABLE 13-6. NUMBER OF BIRTHS BY RACE AND SIZE OF POPULATION[8]

Urban areas of given size from 1970 census	Births			
	White	Black	Others	Total
≥100,000	772.230	321.412	24.394	1.118.036
50-99,999	266.706	37.024	4.182	327.912
10-49,999	600.166	65.790	10.394	676.350
≤9,999	1.432.162	148.136	28.790	1.609.088
Total	3.091.264	572.362	67.760	3.731.386

Urban areas of given size from 1975 census	Births			
	White	Black	Others	Total
≥100,000	571.478	276.387	26.332	874.197
50-99,999	222.735	37.885	5.921	266.541
10-49,999	478.382	64.481	13.039	555.902
≤9,999	1.279.401	132.828	35.329	1.447.558
Total	2.551.996	511.581	80.621	3.144.198

women. There is insufficient evidence at this time to determine whether any racial or ethnic group suffers an innate susceptibility to lead.

In the United States in 1970 about 12 million children under 5 years of age lived in urban areas. Approximately 5 million of these children lived in central city areas.[8] Since between-census population estimates are not available for urban-rural comparisons, the only way to use the 1975 population estimates is to assume that the percent distribution obtained in 1970 still holds true. If in fact that is the case, the more recent estimates would be about 11 million children in urbanized areas and 4.6 million in the central city. An estimate made by the National Bureau of Standards of the total child population with blood lead values equal to or greater than 40 μg/dl in a recent year was 600,000.[10] This total is clearly a cause for concern in view of the health data presented in Section 13.4 above. Of course, the use of this figure, based on the many lead-screening programs conducted in this country, is not meant to imply that all of these values resulted from airborne lead. They probably do not, since paint lead exposures are an additional important source. But, on the other hand, the addition of an airborne component of lead exposure on top of these levels would adversely affect the public health. If airborne lead were the only contribution to these children's lead values, the potential health effects ascribable to that exposure could be significant.

The difficulty in estimating the number of pregnant women exposed to air lead is even greater; this is because the number of pregnant women is not tabulated on an urban-rural basis. Therefore, for this document, the number of pregnant women will be estimated from the number of live births (Table 13-6).[8] Unfortunately these data also are not tabulated on an urban-rural basis but, rather, on a population size of place of residence. It can readily be seen that the total number of births has declined in the time 1970 to 1975. If one assumes only the highest population size category to be at risk of lead exposure, there are still almost 900,000 newborns at risk of lead absorption from their mothers.

13.8 REFERENCES FOR CHAPTER 13

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APPENDIX A
GLOSSARY*

Absorption (of lead): Transfer of lead into an organism via intestinal wall, alveolar surface, or skin.

Accumulation (of lead): Net positive difference between intake and output of lead over an extended period.

Acetyl coenzyme A (CoA): Coenzyme, derived principally from the metabolism of glucose and fatty acids, that takes part in many biological acetylation reactions; oxidized in the Krebs cycle.

Acetylcholine: Compound released from certain autonomic nerve endings; acts in the transmission of nerve impulses to excitable membranes.

Acetylcholinesterase: Enzyme in excitable membranes that inactivates acetylcholine.

β-Acetyl glucosaminadase: Enzyme that hydrolyzes the terminal glucosaminidic bonds of odd-numbered oligosaccharides to yield N-acetylglucosamine and the next lower even-numbered oligosaccharide.

Acid-fast: Describes a cell or bacterium that retains a dye that has a negatively charged molecule.

Acid phosphatase: Enzyme that hydrolyzes, in an acid medium, monophosphoric esters, with liberation of inorganic phosphate.

Adenocarcinoma: Carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures.

Adenoma: Benign epithelial tumor in which the cells form recognizable glandular structures or in which the cells are clearly derived from glandular epithelium.

Adenosine diphosphate (ADP): Coenzyme composed of adenosine and two molecules of phosphoric acid; important in intermediate cellular metabolism; a product of the hydrolysis of adenosine triphosphate (ATP).

Adenosine triphosphate (ATP): Nucleotide occurring in all cells, where it serves in the storage of energy and in the transfer of energy in metabolic processes; composed of adenosine and three molecules of phosphoric acid.

Adenosine triphosphatase (ATPase): Enzyme that mediates the removal of water from ATP: ATP + $H_2O \rightarrow$ ADP + orthophosphate.

Adenyl cyclase: Enzyme that catalyzes the formation of cyclic adenosine-3', 5'-monophosphate (cyclic AMP).

Adenylic acid: (1) Generic name for a group of isomeric nucleotides; (2) Phosphoric acid ester of adenosine; also known as adenosine monophosphate (AMP).

Adrenaline: See Epinephrine.

Adrenergic: Describes the chemical activity of epinephrine or epinephrine-like substances.

Adrenergic synapse: Synapse at which norepinephrine is liberated when a nerve impulse passes.

Advection: Process of transport of an atmospheric property, or substance within the atmosphere, solely by the mass motion of the atmosphere.

Aerodynamic diameter: Expression of aerodynamic behavior of an irregularly shaped particle in terms of the diameter of an idealized particle; that is, aerodynamic diameter is the diameter of a sphere of unit density that has aerodynamic behavior identical to that of the particle in question. Thus, particles having the same aerodynamic diameter may have different dimensions and shapes.

Aerodynamic drag: Aerodynamic resistance; retarding force that acts upon a body moving through a gaseous fluid and that is parallel with the direction of motion of the body.

Aerodynamic particle size: Sphere of unit density that has aerodynamic behavior identical to that of the particle in question.

Aerosol: System in which the dispersion medium is a gas and the dispersed phase—composed of solid particles or liquid droplets—does not settle out under the influence of gravity.

Aerosol particles: Solid particles 10^{-12} to 10^{-1} μm in diameter, dispersed in a gas.

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*Compiled from standard reference works and, to a lesser extent, from information furnished by experts in the respective disciplines.

Agglomeration: Process by which precipitation particles grow by collision with an assimilation of cloud particles or other precipitation particles.

Aitken dust counter: Instrument for determining dust content of the atmosphere; a sample of air is mixed, in an expandable chamber, with a large volume of dust-free air containing water vapor. Upon sudden expansion, the chamber cools adiabatically below its dewpoint, and droplets form with the dust particles as nuclei and are counted by means of a grid under a microscope.

Aitken nuclei: Microscopic particles in the atmosphere that serve as condensation nuclei for droplet growth during the rapid adiabatic expansion produced by an Aitken dust counter (see above).

Aldolase: Enzyme that acts on a ketose-1-phosphate to yield dihydroxy-acetone phosphate plus an aldehyde; e.g., fructose-1, 6-diphosphate = dihydroxyacetone phosphate + D-glyceraldehyde-3-phosphate.

Alkaline phosphatase: Enzyme that hydrolyzes, in alkaline medium, monophosphoric esters, with liberation of inorganic phosphate; found in plasma and serum, bone, etc.

Alkalinity: Excess of hydroxyl ions over hydrogen ions, generally expressed as milliequivalents per liter.

Alveolar macrophages: Rounded granular phagocytic cells, within the alveoli of the lungs, that ingest inhaled material.

Ambient air: The surrounding, well-mixed air.

Aminoacyl synthetase: Enzyme that catalyzes the coupled reactions of amino acid activation in which an amino acid is first attached to adenosine monophosphate and then to a transfer-RNA molecule.

ϵ-Amino group of lysine: The amino group, NH_2, attached to ϵ, or 5th, carbon atom from the carboxyl carbon in the amino acid, lysine: $H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(NH_2)\text{-}COOH$.

δ-Aminolevulinic acid (ALA, or δ-ALA): $COOH\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}CH_2\text{-}NH_2$; intermediate in the biosynthesis of heme-containing compounds; formed from succinyl-coenzyme A and glycine.

δ-Aminolevulinic acid dehydratase (ALAD): Enzyme in heme biosynthetic pathway that mediates formation of porphobilinogen from δ-aminolevulinic acid.

δ-Aminolevulinic acid synthetase (ALAS): Enzyme in heme biosynthetic pathway that mediates the formation of δ-aminolevulinic acid from succinyl-CoA via 2-amino-3-ketoadipate.

Amphetamine: α-Methylphenethylamine. Drug used to stimulate the central nervous system, increase blood pressure, reduce appetite, and reduce nasal congestion. Abuse may lead to dependence, characterized by strong psychic dependence associated with an increase in REM (rapid-eye-movement) sleep, hunger, apathy, and depression.

Anamnestic response: Rapidly increased antibody level following renewed contact with a specific antigen, even after several years.

Anodic stripping voltammetry: An electrochemical method of analysis.

Anophthalmia: Developmental defect characterized by complete absence of the eyes or by the presence of vestigial eyes.

Anorexia: Loss of appetite.

Anoxia: Relative lack of oxygen; caused by inadequate perfusion of tissues by blood carrying normal amounts of oxygen or by normal perfusion of blood carrying reduced amounts of oxygen.

Antipyrine ($C_{11}H_{12}ON_2$): Compound used as an antipyretic, analgesic, and antirheumatic drug.

Area source: Consists of a number of point sources arranged in a two-dimensional array.

Astrocytic proliferation (astrocytosis): Proliferation of astrocytes owing to the destruction of nearby neurons during a hypoxic or hypoglycemic episode.

Ataxia: Failure of muscular coordination.

Atmospheric turbulence: Motion of the air (or other fluids) in which local velocities and pressures fluctuate irregularly in a random manner.

Avoidance task: Behavioral testing procedure used to measure an animal's avoidance and escape performance. In a one-way task only one response is appropriate, whereas in a two-way task either of two responses is appropriate, depending on the existing test conditions.

Axonal degeneration: Degeneration of axons, the processes or nerve fibers that carry the unidirectional nerve impulse away from the nerve cell body.

Balance experiments: Experiments on man or other animals that involve quantitative measurements of intake (via respiration and ingestion) and loss (via exhalation and excretion) of a specific element or substance. A positive balance means that more is taken in than is lost over a specific time.

Basophilic stippling: Spotted appearance of relatively immature red blood cells that contain cytoplasmic material that stains deeply with basic dyes.

Biosphere: The part of the earth's crust, waters, and atmosphere where living organisms can subsist.

Blood-brain barrier: The barrier created by semipermeable cell walls and membranes to passage of some molecules from the blood to the cells of the central nervous system.

Body burden: The total amount of a specific substance (for example, lead) in an organism, including the amount stored, the amount that is mobile, and the amount absorbed.

Bond energy: The enthalpy change that accompanies the breaking of a chemical bond between two atoms. The total bond energy of a molecule gives a measure of its thermodynamic stability.

Boundary layer: Layer of fluid in the immediate vicinity of a bounding surface; refers ambiguously to the (1) laminar, (2) turbulent, (3) planetary, or (4) surface boundary layers.

Brainstem: Stemlike portion of the brain connecting the cerebral hemispheres with the spinal cord.

Bremsstrahlung: Radiation that is emitted by an electron accelerated in its collision with the nucleus of an atom.

Brownian movement: Random movements of dispersed small particles suspended in a fluid; results from random collisions between the molecules of the dispersing medium and the particles of the dispersed phase.

CaEDTA: Edathamil calcium disodium, which is the calcium disodium salt of ethylenediaminetetraacetate, a chelating agent. CaEDTA is used in the study, diagnosis, and treatment of poisoning by various heavy metals, including lead.

CaEDTA mobilization test: Test in which a known quantity of CaEDTA is injected parenterally and the amount of lead excreted in urine during a known period beginning immediately thereafter is measured. This procedure is used both clinically and experimentally and is thought to provide an index of the mobile fraction of the total body burden of lead.

Carcinogenesis: Development of carcinoma; or, in more recent usage, producing any kind of malignancy.

Carcinoma: Malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases.

Cascade impactors: Low-speed impaction device for use in sampling both solid and liquid atmospheric suspensoids; consists of four pairs of jets (each of progressively smaller size) and sampling plates working in series and designed so that each plate collects particles of one size range.

Catalase: Enzyme that catalyzes the decomposition of hydrogen peroxide; contains four hematin groups per molecule; found in liver and red blood cells.

Catecholamines: Group of sympathomimetic amines containing a catechol moiety; especially epinephrine, norepinephrine, and dopamine.

Catenation: Property of an element that enables it to link to itself to form chains, e.g., carbon.

Cerebellum: Large dorsally projecting part of the brain having the special function of muscle coordination and maintenance of equilibrium.

Cerebral anoxia: Relative lack of oxygen in the brain.

Cerebral cortex: Thin layer of gray matter on the surface of the cerebral hemisphere, folded into gyri, with about two-thirds of its area buried in the depths of the fissures.

Chelate: Chemical compound in which a metallic ion is sequestered and bound into a ring by covalent bonds to two or more nonmetallic atoms in the same molecule.

Chelant: Chemical compound that will react with metals to form chelates; a chelating agent.

Cholinergic: Stimulated, activated, or transmitted by acetylcholine; applied to those nerve fibers that liberate acetylcholine at a synapse when a nerve impulse passes.

Cholinesterase: Enzyme that catalyzes the hydrolysis of acylcholine to choline and an anion.

Chemical energy: Energy produced or absorbed in the process of a chemical reaction.

Chi-square test: Test of statistical significance based on frequency of occurrence; used to test probabilities or probability distributions (goodness of fit), statistical dependence or independence (association), and common population (homogeneity).

Chlorinity: Measure of chloride content, by mass (g/kg), of water; sometimes determined to permit calculation of salinity.

Choroid plexus: Any of the highly vascular, folded processes that project into the third, fourth, and lateral ventricles of the brain.

Chromatid: One of the pair of stands, formed by longitudinal splitting of a chromosome, that are joined by a single centromere in somatic cells during mitosis; one of a tetrad of strands formed by lengthwise splitting of paired chromosomes during the diplotene stage of meiosis.

Chromophore: Any chemical group whose presence gives a decided color to a compound and that united with certain other groups to form dyes.

Chromosomes: Threadlike structures in animal or plant nuclei, seen during karyokinesis (nuclear division characteristic of mitosis), that carry the linearly arranged genetic material.

Chronic nephritis: Chronic inflammation of the kidneys.

Coagulation: Process that converts numerous droplets into a smaller number of larger precipitation particles.

Coalescence: Merging of two liquid drops into a single larger drop.

Colic: Paroxysmal pain in the abdomen, caused by spasm, distention, or obstruction of any one of the hollow viscera.

Colloidal materials: See Colloidal system.

Colloidal system: An intimate mixture of two substances, one of which, called the dispersed phase (or colloid), is uniformly distributed in a finely divided state through the second substance (dispersion medium); the dispersion medium may be a gas, liquid, or solid.

Combustion nucleus: Condensation nucleus formed as a result of industrial or natural combustion processes.

Complement: Complex proteins in normal serum that interact to combine with antigen-antibody complex, producing lysis when the antigen is in an intact cell; important in host defense mechanism against invading microorganisms.

Complex: Chemical compound in which a part of the molecular bonding is of the coordinate type.

Complexing: Formation of a complex compound; see Complex.

Condensation: Physical process by which a vapor becomes a liquid or solid; opposite of evaporation. In meteorology, the term is limited to transformation of vapor to a liquid.

Condensation nucleus: Particle, either liquid or solid, upon which condensation of water vapor begins in the atmosphere.

Condensation particles: See Aitken nuclei.

Confidence interval: A range of values ($a_1 < a < a_2$) determined from a sample by definite rules so chosen that, in repeated random samples from the hypothesized population, an arbitarily fixed proportion ($1-\epsilon$) of that range will include the true value, x, of an estimated parameter.

The limits, a_1 and a_2, are called confidence limits; the relative frequency ($1-\epsilon$) with which these limits include α is called the confidence coefficient; and the complementary probability, ϵ, is called the confidence level. As with significance levels, confidence levels are commonly chosen as .05 or .01, the corresponding confidence coefficients being .95, .99.

Confidence intervals should not be interpreted as implying that the parameter itself has a range of values; it has only one value, α. On the other hand, the confidence limits (a_1, a_2), being derived from a sample, are random variables the values of which on a particular sample either do or do not include the true value α of the parameter. However, in repeated samples, a certain proportion (namely $1-\epsilon$) of these intervals will include α_1 provided that the actual population satisfied the initial hypothesis.

Contamination: Contact with an admixture of an unnatural agent, with the implication that the amount is measurable.

Convection: Atmospheric motions that are predominantly vertical, resulting in vertical transport and mixing of atmospheric properties.

Convulsions: Violent, involuntary contraction or series of contractions of the voluntary muscles.

Coprogen III: Coproporphyrinogen III, an intermediary metabolite in heme biosynthesis. It is a natural precursor of heme.

Coprogenase: Coproporphyrinogenase, the enzyme that converts coproporphyrinogen III to protoporphyrin IX.

Coproporphyrin: Urinary pigment derived from coproporphyrinogen, an intermediate in the biosynthesis of heme.

Coproporphyrinogen (syn. coprogen): A fully reduced colorless tetracarboxylic tetrapyrrole. Isomers I and III are found in biologic systems.

Cortex: See Cerebral cortex.

Corpus callosum: Band of nerve tissue connecting the cerebral hemispheres in man and higher mammals.

Corpus striatum: A subcortical mass of gray and white substance in each cerebral hemisphere, containing the caudate nucleus and the lentiform nucleus.

Cortical atrophy: Wasting away of the outer layer(s), e.g., of the brain or kidney.

Creatinine: $C_4H_2ON_3$; compound formed by dehydration of creatine; found in urine, blood, and muscle.

Cristae: Inner membranes of mitochondria, the surfaces of which are studded with roughly spherical particles attached to the cristae by stalks.

Cumulative frequency distribution: Proportion of a distribution that lies below a given value.

Curie: Unit of radioactivity; quantity of radionuclide that has 3.7×10^{10} disintegrations per minute (dpm).

Cysteine: Amino acid that occurs as a constituent of glutatione and of cystine.

Cytochrome *c*: Small heme protein containing one atom of iron per molecule; its principal biologic function is in electron transport. See Cytochromes.

Cytochrome *c* oxidase (cyt. a_3): Enzyme that catalyzes the oxidation of cytochrome *c*: 4 reduced cytochrome $c + O_2 = 4$ oxidized cytochrome $c + 2H_2O$.

Cytochrome *c* reductase: Enzyme that catalyzes the reduction of oxidized cytochrome *c*: $NADH_2 +$ oxidized cytochrome $c = NAD +$ reduced cytochrome *c*.

Cytochrome P-450: a *b*-type cytochrome, one of the mixed-function oxidases in the microsomal system responsible for the oxidation of steroids and drugs and other foreign compounds.

Cytochromes: Complex protein/heme respiratory pigments occurring in plant and animal cells, usually in mitochondria, that function as electron carriers in biological oxidation.

Demyelination: Destruction of the myelin, a fatlike substance forming a sheath around the nerve fibers.

Density: Ratio of mass of a substance to the volume occupied by it (usually expressed in g/cm^3).

Dentine: Also dentin; chief substance or tissue of the teeth, that surrounds the tooth pulp and is covered by enamel on the crown and by cementum on the roots of the teeth.

Denver Development Screening Test: Rating scales employed to assess four areas of child development: (1) gross motor, (2) fine motor-adaptive, (3) personal-social, and (4) language.

Deoxyribonucleic acid (DNA): A nucleic acid in the form of a doublestranded helix of a linear polymer; made up of repeating units of 2-deoxyribose, phosphate, and a purine or a pyrimidine; carrier of genetic information coded in the sequence of purines or pyrimidines (organic bases).

Deposition: (1) Deposit of particles from the ambient air or atmosphere onto a surface; (2) removal of particles from inhaled air by the respiratory tract.

Detection limit: A limit below which an element or compound can not be detected by the method or instrument being used for analysis.

Dichotomous sampler: Air-sampling device that separates particulates into two fractions on the basis of diameter; the cutpoint varies with the size of the aperture.

Diffusion: In meteorology, the exchange of fluid parcels between regions in space in apparently random small-scale motions.

p-Dimethylaminobenzaldehyde: Ehrlich's reagent; $(CH_3)_2N{\cdot}C_6H_4{\cdot}CHO$.

Diphenylthiocarbazone: See Dithizone.

Dispersion: Distribution of finely divided particles in a medium.

Dithizone: Diphenylthiocarbazone; $C_6H_5N{:}N\text{-}CS\text{-}NH{\cdot}NH\text{-}C_6H_5$; reagent used in the analysis of lead.

Dithizone methods: Colorimetric methods of analysis for lead that involve the reaction of lead with dithizone to form lead dithizonate, which is measured spectrophotometrically at 510 nm.

Dopamine: Hydroxytyramine, produced by the decarboxylation of dopa (dihydroxyphenylalanine), which is an intermediate product in the synthesis of norepinephrine.

Dorsal root ganglion: Group of sensory nerve cell bodies located on the posterior root of each spinal nerve; joins peripherally with ventral, or motor, root to form the nerve before it passes outside the vertebral column.

Downwind: In the same direction that the wind is blowing; on or toward the lee side.

Dry deposition: The deposit of particles on a surface in the absence of precipitation.

Dust: Solid materials suspended in the atmosphere in the form of small irregular particles, many of which are microscopic in size.

Dustfall: Dry deposition of airborne dust particles.

Dysoria: Any abnormality of vascular permeability.

E. coli: Short, gram-negative, rod-shaped, enteric bacterium.

Edema: Presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body; usually applied to the demonstrable accumulation of excessive fluid in the subcutaneous tissues.

Electromyographic: Pertaining to electromyography, the recording and study of the intrinsic electrical properties of skeletal muscle.

Electron microprobe: X-ray method in which electrons from a hot-filament source are accelerated electrostatically, then focused to an extremely small point on the surface of a specimen by an electromagnetic lens; method for nondestructive analysis of chemical composition by measurement of resulting backscatter or other phenomena.

Electronegativity: Electro-affinity.

Encephalitis: Inflammation of the brain.

Encephalopathy: Any degenerative disease of the brain.

Epidemiology: Study of the distribution and determinants of disease in human population groups.

Epinephrine: Hormone secreted by adrenal medulla that acts to increase blood pressure by means of stimulation of heart action and constriction of peripheral blood vessels.

Episodal: Adjective in current usage that denotes an air pollution episode; that is the occurrence of short-term, peak air pollutant concentrations of crisis proportions.

Epithelial: Pertaining to or composed of epithelium; that is, covering of external or internal body surfaces, including linings of vessels and other small cavities, composed of cells joined together with cementing substances.

Equilibrium vapor pressure: Vapor pressure of a system in which two or more phases of a substance coexist in equilibrium.

Erosion: Movement of soil or rock from one point to another by the action of the sea, running water, moving ice, precipitation, or wind.

Erythrocyte porphyrin: See Free erythrocyte protoporphyrin.

Erythrocyte protoporphyrin: See Free Erythrocyte portoporphyrin.

Erythrocytes: Red blood cells.

Erythropoiesis: Formation of red blood cells.

Ethylenediaminetetraacetic acid (EDTA): Used in the form of calcium-disodium salt as a chelating agent to complex with lead and other metals and remove them from the body by urinary excretion.

Evaporation: Physical process by which a liquid or solid is transformed to the gaseous state; opposite of condensation.

Evoked-response technique: A technique widely used in electrophysiology in which a stimulus (e.g., electric shock, light flash, click) is applied peripherally to the electrode used to detect the response.

Exencephaly: A developmental anomaly characterized by an imperfect cranium, the brain lying outside the skull.

Exposure level: Concentration of a contaminant to which the population in question is exposed.

Exudate: Material, such as fluid, cells, or cellular debris, that has escaped from blood vessels and has been deposited in tissues or on tissue surfaces, usually as a result of inflammation; contains high content of protein, cells, or solid materials derived from cells.

Fallout: In air pollution, particulate matter that falls to the surface of the earth through the action of gravity; a passive phenomenon unrelated to atmospheric or mechanical motion.

Fanconi syndrome: In this document, the triad of glycosuria, hyperaminoaciduria, and hypophosphatemia in the presence of hyperphosphaturia that is associated with injury to proximal renal tubular cells.

Flinch/jump thresholds: Behavioral testing procedure used to measure pain threshold by measuring sensitivity to shock. The shock intensity at which animals first flinch and first jump in response to foot shock is recorded.

Flux: Rate of flow of some quantity, often used in reference to some form of energy; also called transport.

Fornix: General term for an archlike structure or the vaultlike space created by such a structure; fornix of cerebrum—efferent pathway of the hippocampus.

Free erythrocyte porphyrin (FED): See Free erythrocyte protoporphyrin.

Free erythrocyte protoporphyrin (FEP): Intermediate in the biosynthesis of heme; specifically, the immediate precursor to heme synthesis in which one atom of iron is inserted into the protoporphyrin nucleus to form heme. Used interchangeably with erythrocyte protoporphyrin and erythrocyte porphyrin.

Fugitive dust: Dust that escapes from industrial processes, soil surfaces, roadways, etc.; dust that cannot be contained by air pollution control practices.

β-Galactosidase: Enzyme that hydrolyzes galactosides (compounds containing a sugar and a nonsugar component) to produce D-galactose.

Galena: Lead sulfide ore.

Ganglia: Plural of ganglion, a general term for a group of nerve cell bodies located outside the central nervous system; basal ganglia—masses of gray matter in the cerebral hemisphere.

Gastrointestinal mucosa: Mucous membrane of the stomach and intestine.

Geometric mean: An estimate of the median of a lognormal distribution, calculated as the antilogarithm of the mean of the logarithms of the observations.

Geometric standard deviation: A measure of dispersion for a lognormal distribution; it is the antilogarithm of the standard deviation of the logarithms of the observations. (Also known as standard geometric deviation.)

Glacier: Mass of land ice flowing slowly (at present or in the past) from an accumulation area to an area of ablation.

Glacier ice: Any ice that is or once was part of a glacier.

Glomerular filtration: Filtration of plasma by the glomeruli of the kidney that removes fluids, electrolytes, glucose, amino acids, and other small molecules; 80 to 85 percent of water and virtually all of the other substances are reabsorbed by the proximal tubules.

Glomerulus: Anatomical term designating a tuft or cluster of blood vessels or nerves; often used alone to designate renal glomeruli, which are coils of blood vessels, one projecting into the expanded end or capsule of each of the uriniferous tubules of the kidney.

Glucose-6-phosphate dehydrogenase: Enzyme important in maintenance of adequate concentrations of reduced glutathione in red blood cells. Deficiency of this enzyme is inherited as a sex-linked trait; it mediates the reaction, D-glucose-6-phosphate + NADP = D-glucono-δ-lactone 6-phosphate + $NADPH_2$.

β-Glucuronidase: Enzyme that mediates the hydrolysis of natural and synthetic glucuronides; yields β-D-glucuronate as a product.

Glutamate dehydrogenase: Enzyme that mediates the removal of hydrogen atom(s) from glutamate, the salt or ester of glutamic acid, which is a dicarboxylic amino acid.

Glutathione: Tripeptide that serves as a coenzyme and acts as a respiratory carrier of oxygen. Reduced glutathione (GSH) is present in red cells and is associated with glucose-6-phosphate dehydrogenase and reduced nicotinamide adenine dinucleotide phosphate in maintenance of red cell integrity.

Glycosuria: Presence in the urine of glucose, a simple sugar formed from more complex sugars and normally retained in the body as a source of energy.

Grignard process: A relatively common synthetic procedure for the preparation of organometallic compounds from an organomagnesium precursor.

Groundwater: All subsurface water, especially that part that is in the zone of saturation.

Half-life: Time required for a system decaying at an exponential rate (such as an element in radioactive disintegration) to be reduced to one-half its initial size, intensity, or numerical amount.

Haze: Fine dust or salt particles dispersed through a portion of the atmosphere; the particles are so small they cannot be felt or individually seen with the naked eye, but they diminish horizontal visibility and give the atmosphere a characteristic opalescent appearance that subdues all colors.

Hematofluorometer: Commercially available portable spectrofluorometer used to measure erythrocyte protoporphyrin (porphyrin) directly; in wide use in lead screening programs.

Hematopoiesis: Formation and development of blood cells.

Hematopoietic system: System of cells in bone marrow, spleen, and lymph nodes concerned with formation of cellular elements of the blood.

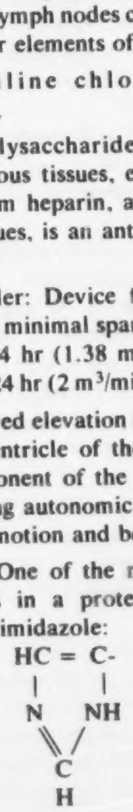
Hemin: Crystalline chloride of heme, $C_{34}H_{33}N_4O_4FeCl$.

Heparin: Mucopolysaccharide acid occurring naturally in various tissues, especially the liver and lungs; sodium heparin, a mixture obtained from animal tissues, is an anticoagulant used *in vivo* and *in vitro*.

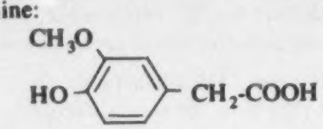
High-volume sampler: Device for taking a large sample of air in a minimal span of time, routinely about 2000 m^3/24 hr (1.38 m^3/min), or even as high as 2880 m^3/24 hr (2 m^3/min).

Hippocampus: Curved elevation in the inferior horn of the lateral ventricle of the brain; important functional component of the limbic system, the system controlling autonomic functions and certain aspects of emotion and behavior.

Histidine residue: One of the naturally occurring peptide linkages in a protein, containing the chemical group, imidazole:



Homovanillic acid: A methylated metabolite of hydroxytyramine:



Hydrocephalus: Condition characterized by abnormal accumulation of fluid in the cranial vault, accompanied by enlargement of the head, prominence of the forehead, atrophy of the brain, mental deterioration, and convulsions.

Hyperactivity: Abnormally increased activity. Developmental hyperactivity of children is characterized by constant motion—exploring, experimenting, etc.—and is usually accompanied by distractibility and low tolerance for frustration. It usually abates during adolescence. May result from brain damage or psychoses.

Hyperkinesia: Abnormally increased motor function or activity; see Hyperactivity.

Hyperkinetic: Characterized by abnormally increased muscular movement.

Hyperkinetic-aggressive behavior disorder: A disorder characterized by overactivity, restlessness, distractibility, and short attention span.

Hyperphosphaturia: Above-normal amounts of phosphate compounds in the urine.

Hyperuricemia: Abnormal amounts of uric acid in the blood.

Hypochromic anemia: A condition characterized by a disproportionate reduction of red cell hemoglobin, compared with the volume of packed cells.

Hypophosphatemia: Abnormally decreased amount of phosphates in the blood.

Hypothalamus: Portion of the diencephalon that forms the floor and part of the lateral wall of the third ventricle of the brain.

Imidazole group: See Histidine residue.

Impactor: General term for instruments that sample atmospheric particles by impaction; such devices consist of a housing that constrains the air flow past a sensitized sampling plate.

Impinger: Device used to sample dust or other particles in the air; draws in a measured volume of air and directs it through a jet to impact on a wetted surface.

In situ: In the original location.

Interstitial fibrosis: A progressive formation of fibrous tissue in the interstices in any structure; in the lungs, it reduces aeration of the blood.

In vitro: Outside the living organism.

In vivo: Within the living organism.

Iron deficiency: A deficiency of iron-containing foods in the diet such that not enough iron is available for incorporation into newly formed hemoglobin; iron deficiency within the body may also result from poor intestinal absorption of iron in spite of a dietary sufficiency.

Ischemia: Deficiency of blood in a part, caused by functional constriction or actual obstruction of a blood vessel.

Ischemic: Pertaining to, or affected with, ischemia.

Isocortex: Neopallium; that portion of the cerebral cortex showing stratification and organization characteristic of the most highly evolved type of cerebral tissue.

Isokinetic sampling: Taking a sample of air without changing the speed or direction of the air as it enters the sampler.

Jiggle platform: Apparatus used in behavioral testing to measure an animal's activity. Generally consists of a spring-loaded platform equipped with a detector for measuring movement.

α-Ketoglutarate: Salt of α-ketoglutaric acid, a dibasic keto acid occurring as an intermediate in carbohydrate (Krebs cycle) and protein metabolism.

Kilocalorie: Unit of heat energy equal to 1000 calories; also known as large calorie.

Lactic acid dehydrogenase (LDH): Catalyzes reduction of pyruvic acid by reduced nicotinamide adenine dinucleotide; prevents buildup of pyruvate in anaerobic glycolysis.

Leached: Subjected to the action of percolating water or other liquid that removes the soluble substances.

Lead particles: Lead-containing particles.

Lead poisoning (syn. lead intoxication, plumbism, saturnism): A disease condition reflecting the adverse effects of the absorption of lead into the system.

Lead subacetate (syn. lead monosubacetate, monobasic lead acetate): $Pb(C_2H_3O_2)_2 \cdot 2Pb(OH)_2$.

Learning paradigm: A particular set of experimental conditions used to study learning.

Ligand: A molecule, ion, or atom that is attached to the central atom of a coordination compound, a chelate, or other complex.

Line source: Consists of a number of point sources arranged in a straight line, usually across wind (see Point source).

Lipoamide dehydrogenase: Trivial name for lipoamide oxidoreductase; enzyme catalyzing the reaction, NAD + dihydro-lipoamide = $NADH_2$ + oxidized lipoamide.

Lithosphere: The rigid outer crust of rock on the earth, about 80 km deep; more recently, with development of plate tectonics theory, the outer 100 km of the earth's surface.

Lognormal distribution: A variable whose logarithms follow a normal distribution.

Lumen: The cavity or channel within a tubular organ; in this document, intestinal.

Lymphocyte: Mononuclear leukocyte (a white blood cell) with a deeply staining nucleus containing dense chromatin; chiefly a product of lymphoid tissue, it participates in humoral and cell-mediated immunity.

Lysosome: Submicroscopic organelle, found by electron microscope in many types of cells, that contains various hydrolytic enzymes and is normally involved in localized intracellular digestion.

α-Mannosidase: Enzyme that catalyzes the hydrolysis of α-D-mannoside to an aocohol and D-mannose, a simple sugar.

Mass median diameter (MMD): Geometric median size of a distribution of particles, based on weight.

Mass median equivalent diameter (MMED): Convenient parameter for characterizing airborne particulates; divides the total mass of aerosol particles into two equal parts: half the mass resides in a relatively smaller number of particles larger than this median size and half resides in a relatively larger number of particles having diameters below this median size.

Maze: System of intersecting paths used in tests of intelligence and learning in experimental animals.

McCarthy Scales of Intelligence: A standardized intellectual assessment instrument (appropriate for ages 2.5 to 8.5 yr), consisting of five subtests yielding individual scores in (1) verbal, (2) perceptual-performance, (3) quantitative, (4) memory, and (5) motor, as well as yielding a general cognitive index comparable to an intellectual quotient (I.Q.) score.

Mean: Used synonymously with the arithmetic mean; that is, the sum of the observations divided by the sample size.

Meninges: Three membranes that envelope the brain and spinal cord; the dura mater, pia mater, and arachnoid.

Messenger RNA (mRNA): Linear polymer of nucleotides that is transcribed from and complementary to a single strand of DNA; carries information for protein synthesis to the ribosomes.

Metabolites: End products of metabolic processes that transform one compound into another in living cells.

Microcytic anemia: Condition in which the majority of the red cells are smaller than normal.

Micromelia: Developmental anomaly characterized by abnormal smallness or shortness of the limbs.

Microsome: One of the finer granular elements of protoplasm; part of the endoplasmic reticulum, site of various metabolic and synthetic processes including incorporation of amino acids into proteins.

Mist: Microscopic and more or less hygroscopic water droplets suspended in the atmosphere. Relative humidity when mist is present is often less than 95 percent.

Mitochondria: Small organelles found in the cytoplasm of cells; principal sites of generation of energy, they contain enzymes of the Krebs and fatty acid cycles and the respiratory pathway.

Mobilizable lead: The fraction of the total lead content of the body that can be removed by chelating agents.

Molal: Containing one mole or one gram molecular weight in 1000 grams (1 kg) of solute.

Molar: Containing one mole or one gram molecular weight of solute in 1000 ml (1 liter) of solution.

Mole: That amount of chemical compound whose mass in grams is equivalent to its formula mass, i.e., mass numerically equal to the molecular weight and most frequently expressed as the gram molecular weight (the weight of one mole expressed in grams).

Midbrain: Mesencephalon; portions of the adult brain derived from the embryonic midbrain.

Miniature end-plate potentials (MEPP's): Small potential changes in the neighborhood of the end plate representing the response of the membrane to release of acetylcholine in quantities insufficient to depolarize the membrane to threshold levels.

Monoamine: Organic compound to which an amine ($-NH_2$ group) is attached; e.g., serotonin.

Monamine oxidase: Flavoprotein that catalyzes the aerobic oxidation of physiological amines to the corresponding aldehydes and ammonia; acts upon serotonin, a nervous system regulator, to yield 5-hydroxy-indolealdehyde.

Monominergic: Stimulated, activated, or transmitted by monoamines; applied to nerve fibers that liberate monoamines at a synapse when a nerve impulse passes.

Motor skills: Skilled movements that depend on the integrity of the nervous system for control.

Mutagenicity: Property of being able to induce genetic mutation, i.e., a permanent, transmissable change in the genetic material.

Myelopathy: Pathology of the muscle fibers.

Myxedema: Nonpitting edema characterized by dry, waxy type of swelling, with abnormal deposits of mucin in the skin and other tissues; associated with hypothyroidism.

Nasopharynx: The part of the pharynx that lies above the level of the soft palate; the pharynx being the muscular, membranous sac between the mouth, the nares, and the esophagus.

National Air Surveillance Networks (NASN): Networks of monitoring stations for sampling air to determine extent of pollution. Established jointly by Federal and state governments.

Neoplasm: An aberrant new growth of abnormal cells or tissue in which the growth is uncontrollable and progressive.

Nephritis: Inflammation of the kidney.

Nephropathy: Disease of the kidneys.

Nerve conduction: Passage of a nerve impulse manifested by an electric impulse that travels along the nerve.

Neuropathy: Functional disturbances and/or pathological changes in the peripheral nervous system; affects the neurons (nerve cells, including cell body, axon, and dendrites).

Neuropil: Dense feltwork of interwoven cytoplasmic processes of nerve cells and of neuroglial cells in the central nervous system and in some parts of the peripheral nervous system.

Nictitating membrane: Thin membrane, or inner or third eyelid, present in many animals; capable of being drawn across the eyeball, as for protection.

Norepinephrine: Hormone secreted by neurons; acts as a transmitter substance at the peripheral sympathetic nerve endings and probably in certain synapses in the central nervous system.

Normal distribution (Gaussian distribution): Fundamental frequency distribution of statistical analysis. A continuous variate, x, is said to have a normal distribution or to be normally distributed if it possesses a density function, f(x), that satisfied the equation:

$$f(x) = \frac{1}{\sigma 2\pi} e^{-(x-\mu)^2/2\sigma^2} \quad (-\infty < x < \infty),$$

where μ is the arithmetic mean (or first moment) and σ is the standard deviation. About two-thirds of the total area under the curve is included between $x = \mu - \sigma$ and $x = \mu + \sigma$.

Normal population: Collection of quantities having a normal distribution.

Normoblast: Nucleated percursor cell intermediate in the formation of erythrocytes.

Nuclear inclusion bodies: Round, oval, or irregularly shaped bodies appearing in the nuclei of cells.

Nucleus: Small mass of differentiated protoplasm rich in nucleoproteins and surrounded by a membrane; found in most animal and plant cells; contains chromosomes and functions in metabolism, growth, and reproduction.

One-way avoidance tasks: See Avoidance task.

Optical emission spectrography: Analytical method in which the sample is vaporized and decomposed, and the constituent elements excited by an electrical arc or a high voltage spark. The light emitted as a consequence of the excitation passes through a spectrograph and the resulting spectrum is recorded photographically.

Paraplegia: Paralysis of the legs and lower part of the body.

Parenchyma: General term to designate functional elements of an organ as distinguished from its framework, or stroma.

Particle eddy diffusivity: The diffusion of particles by eddies in a turbulent flow.

D-penicillamine: Product of penicillin; whitish crystalline powder used as a metal complexing agent to remove excess metals from the body.

Peptidergic: Stimulated, activated, or transmitted by peptides; applied to those nerve fibers that liberate peptides at a synapse when a nerve impulse passes.

Photolysis: Chemical decomposition by the action of light.

Phrenic nerve: Arising from the third, fourth, and fifth cervical segments of the spinal cord, the nerve that innervates the diaphragm.

Pica: Habitual ingestion of nonfood items.

Pinna: Projecting part of the ear lying outside the head.

Plumbism: Lead poisoning; saturnism.

Point source: A single isolated stationary source of pollution.

Polarography: An electroanalytical technique in which the current through an electrolysis cell is measured as a function of the applied potential.

Polyneuropathy: Disease that involves several nerves.

Polysomes: Complex of ribosomes bound together by a single messenger ribonucleic acid (mRNA) molecule. Also known as polyribosome.

Porphobilinogen (PBG): Intermediate in the biosynthesis of heme that does not accumulate under normal circumstances.

Porphyrin: Any one of a group of iron-free or magnesium-free cyclic tetrapyrrole derivatives that occur universally in protoplasm. They form the basis of the respiratory pigments, such as cytochromes and chlorophyll, of animals and plants.

Precipitation: Any or all forms of water particles, liquid or solid, that fall from the atmosphere and reach the ground.

Prevailing wind direction: Wind direction most frequently observed during a given period.

Primary smelting: Extraction of metal from ore.

Promotional energy: Energy required to promote an electron from its free atom ground state to the hybridization state required for bonding.

Protoporphyrin (PP): Porphyrin that is the protein-free precursor to hemoglobin, myoglobin, catalase, and certain respiratory pigments.

Protoporphyrin IX: An isomer of protoporphyrin.

Proximal convoluted tubules: Convoluted portion of the vertebrate nephron (functional unit of the kidney) lying between Bowman's capsule and the loop of Henle; functions in resorption of sugar, Na^+, Cl^-, and water.

Psychomotor: Pertaining to motor effects of cerebral or psychic activity.

Pyrimidine-5'-nucleotidase: Enzyme that mediates hydrolysis of pyrimidine-5'-phosphate to yeild inorganic phosphorus and the corresponding pyrimidine nucleoside.

Pyrrole: Heterocyclic ring compound, consisting of four carbon atoms, one nitrogen atom, and five hydrogen atoms, that is a component of chlorophyll, hemin, and many other important naturally occurring substances.

Pyruvate: Salt of pyruvic acid, an important intermediate in carbohydrate (Krebs cycle) and protein metabolism.

Reentrainment: Resuspension of particulate matter, especially dust, in the ambient air; see text dicussion of resuspension.

Reference method: In this document, the official, accepted method for sampling and analysis of an element or compound; method to which other methods are compared for accuracy and precision, and/or for reporting of data.

Relative humidity: Dimensionless ratio of actual vapor pressure of the air to the saturation vapor pressure; usually expressed as percent.

Renal insufficiency: State in which the kidneys are unable to remove a sufficient proportion of the effete, or spent, matter of the blood.

Reticulocytosis: Increase in the number of reticulocytes (young red blood cells showing basophilic network under vital staining) in the peripheral blood.

Ribonucleic acid (RNA): Nucleic acid in the form of a linear polymer, usually a single strand, composed of repeating units of nucleotides (the organic bases; adenine, cytosine, guanine, and uracil) conjugated to ribose and kept in sequence by phosphodiester bonds. Involved intracellularly in protein synthesis.

Ribosomes: Complex small particles in the living cell, composed of various proteins and three molecules of RNA; site of synthesis of proteins.

Sampling error: Difference between a measured value and the true value that results from sampling techniques and procedures.

Sampling train: Pollutant collecting device consisting of a series of components through which an air stream passes. Components usually include prefitter; pipes or ducts; means for measuring air flow; an air pump; and a detector or sensor that gives an immediate reading *or* a collector in which the pollutant is subsequently measured.

Saturnism: Lead poisoning.

Schwann cell: One of the large nucleated masses of protoplasm lining the inner surface of the neurilemma, a membrane wrapping the nerve fiber.

Secondary smelting: Extraction of metal from scrap and salvage.

Sedimentation: The act or process of deposition of sediment; can refer (1) to the deposition of airborne particulate matter on a surface or (2) to the deposition and accumulation of solid matter on the bed of a body of water.

Seizure: Sudden onset or recurrence of a disease or an attack; specifically, an epileptic attack, or convulsion.

Septum-frontal forebrain: Describes anatomical connections in the brain between the septal area and the forebrain.

Sequela: Any lesion or affection that follows or is caused by an attack of disease.

Serotonin: A vasoconstrictor, 5-hydroxytryptamine, found in serum and many body tissues, including the intestinal mucosa, pineal body, and central nervous system, especially the hypothalamus, midbrain, basal ganglia, and spinal cord; believed to be a neurotransmitter that plays a regulatory role in the central nervous system.

Serum glutamic-oxaloacetic transaminase (SGOT): Enzyme that transfers an amino group from L-glutamic acid to oxaloacetic acid, forming δ-ketoglutaric acid plus L-aspartic acid. Oxaloacetic and δ-ketoglutaric acids are both major intermediates in the citric acid cycle (Krebs cycle), the energy-generating cycle.

Serum glutamic-pyruvic transaminase (SGPT): Enzyme that transfers an amino group from L-glutamic acid to pyruvic acid, forming δ-ketoglutaric acid plus L-alanine. δ-Ketoglutaric acid is a major intermediate in the Krebs cycle, and pyruvic acid is the immediate precursor of acetylcoenzyme A, which combines with oxaloacetic acid to form citric acid in the citric acid cycle (Krebs cycle).

Shuttle box: Two-compartment chamber used in animal behavior; the movement from one compartment to the other is the behavior that is studied.

Soret band: Band in the violet end of the spectrum of hemoglobin.

Spina bifida: Developmental anomaly characterized by defective closure of the bony encasement of the spinal cord.

Stabilimeter: Device used to measure an animal's activity by measuring vertical movement of the floor.

Stack emissions: Effluents released into the atmosphere from the exhaust flue of a building; usually refers to pollutants but can refer to steam or other nonpolluting effluents.

Standard deviation: A measure of dispersion or variation, usually taken as the square root of the variance.

Standard geometric deviation: Measure of dispersion of values about a geometric mean; the portion of the frequency distribution that is one standard geometric deviation to either side of the geometric mean accounts for 68 percent of the total samples.

Standard normal deviation: Measure of dispersion of values about a mean value; the positive square root of the average of the squares of the individual deviations from the mean.

Stanford-Binet I.Q. Test: A standardized intellectual assessment instrument (appropriate for ages 2 yr to adult), yielding a general intelligence quotient (I.Q.) score.

Steady state exposure: Exposure to an environmental pollutant whose concentration remains constant for a period of time.

Stoichiometry: Numerical relationship of elements and compounds as reactants and products in chemical reactions.

Stratosphere: Atmospheric shell about 55 km deep that begins where the troposphere ends, at 10 to 20 km from the earth's surface.

Striatum: Corpus striatum; subcortical mass of gray and white substance in front of and lateral to the thalamus in each cerebral hemisphere.

Stroma: Supporting tissue or matrix of an organ, as distinquished from its functional element, or parenchyma.

Subclinical lead poisoning: Toxic effects of lead that do not produce clinically discernible signs.

Succinate: Salt of succinic acid, important intermediate in carbohydrate (Krebs cycle) and protein metabolism.

Succinoxidase: Complex enzyme system, containing succinic dehydrogenase and cytochromes, that catalyzes the conversion of succinate and molecular oxygen to fumarate (a Krebs cycle intermediate).

Succinyl coenzyme A: $\mathrm{COOH(CH_2)_2COOH\text{-}S\text{-}CoA}$; compound formed from succinic acid and coenzyme A in the citric acid cycle (Krebs cycle). It provides free energy for the synthesis of a molecule of ATP and can participate in acylating reactions for the introduction of a succinyl group; it also participates in other metabolic reactions, such as the synthesis of porphyrins.

Sulfhydryl group: The -SH group occurring in reduced glutatione and in cysteine.

Superior cervical ganglion: A group of nerve cell bodies located outside the central nervous system, situated near the cervix.

Surface water: All bodies of water on the surface of the earth.

Synapse: Region of contact between processes of two adjacent neurons.

Synaptic uptake: Movement of a chemical into the neuron in the area of the synapse.

Synaptosomal transport: Uptake of a chemical into isolated synapses.

Synergetic: Working together; an agent that works synergistically with one or more other agents.

Synergistic effects: Joint effects of two or more agents, such as drugs that increase each other's effectiveness when taken together.

Telencephalon: Paired cerebral vesicles, from which the cerebral hemispheres are derived.

Teratology: Science that deals with abnormal development of the fetus and congenital malformations.

Teratospermia: Presence of malformed spermatozoa in the semen.

Temperature inversion: Layer of air in which temperature increases with altitude; very little turbulent exchange occurs within it.

Terminal velocity: See Terminal fall velocity.

Terminal fall velocity (terminal velocity): Particular falling speed, for any given object moving through a fluid medium of specified physical properties, at which the drag forces and buoyant forces exerted by the fluid on the object just equal the gravitational force acting on the object, after which it falls at constant speed unless it moves into air layers of different physical properties. In the atmosphere, the latter effect is so gradual that objects such as raindrops, which attain terminal velocity at great heights above the surface, may be regarded as continuously adjusting their speeds to remain at all times essentially in the terminal fall condition.

Topography: (1) General configuration of a surface, including its relief; may be a land or water-bottom surface; (2) natural surface features of a region, treated collectively as to form.

Transaminases: Enzymes that catalyze the transfer of an amino group of an amino acid to a keto acid to form another amino acid; also known as aminotransferases.

Transfer RNA (tRNA): Smallest ribonucleic acid molecule found in cells; its structure is complementary to messenger RNA and it functions in transferring amino acids from their free state to a growing polypeptide chain.

Transformation: In this document, changes in physical or chemical form of lead-containing particles or compounds that occur with time and space during atmospheric and environmental residence and/or transport.

Translocation: Transfer of metabolites, nutritive materials, or other substances from one part of a plant to another.

Transport: In this document, movement of lead and its compounds from one place to another in the environment.

Transudation: Passage of serum or other body fluid through a membrane or tissue surface; may or may not be the result of inflammation.

Troposphere: The atmospheric shell extending about 10 to 20 km from the earth's surface.

Trypan Blue: An acid, azo dye used in vital staining; under normal conditions, it does not enter most areas of the brain from the blood.

Tumor: Any abnormal mass of cells resulting from excessive cellular multiplication.

Turbulence: State of fluid flow in which instantaneous velocities exhibit irregular and apparently random fluctuations so that, in practice, only statistical properties can be recognized and analyzed; turbulence can transport suspended matter at rates far in excess of rates of transport by diffusion and conduction in a laminar flow.

Two-way aviodance tasks: See Avoidance task.

Tyrosine: Amino acid (*p*-hydroxyphenylalanine, $C_9H_{11}O_3N$) found in most proteins and synthesized metabolically from phenylalanine. It is a precursor of dopamine and of the hormones, epinephrine, norepinephrine, and triiodothyronine.

Ultradian rhythms: Biological rhythm with a frequency higher than circadian (24 hr).

Uncertainty: Standard deviation of a sufficiently large number of measurements of the same quantity by the same instrument or methods; the noncorrectable inaccuracy of the instrument.

Upwind: Toward the direction from which the wind is flowing; counter to the wind.

Urobilinogen: Colorless compound formed in the intestine by the reduction of bilirubin (a bile pigment that is a breakdown product of heme); some is excreted in the feces where it is oxidized to urobilin; some is reabsorbed and reexcreted in the bile (as bilirubin) or in the urine.

Uroporphyrin: Any of several isomeric, metal-free porphyrins, occurring in small quantities in normal urine and feces.

Vacuolization: Formation of vacuoles, any small spaces or cavities formed in the protoplasm of a cell.

Vacutainers: Registered trademark of sealed ampules, maintained under a slight vacuum and containing an anticoagulant, into which blood samples may be drawn directly.

Vanillyl mandelic acid (vanilmandelic acid): A major metabolite of the catechloamines; used to assess quantitatively the endogenous production of catecholamines.

Variance: A measure of dispersion or variation of a sample from its expected value. It is usually calculated as a sum of squared deviations about a mean divided by the sample size.

Wechsler Inteiligence Test (WISC): A standardized intellectual assessment instrument (appropriate for ages 6 yr to 16 yr 11 mo), consisting of 12 subtests designed to yield verbal and performance intellectual scores.

Wet deposition: Removal of particles from the atmosphere via precipitation; rainout.

Wind: Air motion relative to the surface of the earth. Vertical components are relatively small, especially near the surface of the earth; hence, the term denotes almost exclusively the horizontal component.

WPPSI Test: A version of the WISC test, but consisting of 10 subtests representing a downward extension of the WISC appropriate for younger children (ages 4 to 6.5 yr).

Xenobiotics: Chemicals foreign to biologic systems.

X-ray diffraction analysis: Analysis of the crystal structure of materials by passing Xrays through them and registering the diffraction (scattering) image of the rays.

X-ray powder diffraction techniques: Analytical techniques in which an X-ray beam of known wavelength strikes a finely ground powder sample; the crystal planes of the powder diffract the beam and these diffraction lines are recorded on photographic film.

X-ray spectrography: Analytical method employing an X-ray spectrometer (instrument for producing the X-ray spectrum of a material and measuring the wavelengths of components) that is equipped with photographic or other recording apparatus.

Zinc erythrocyte porphyrin: The biochemically correct form for the erythrocyte protoporthyrin or porphyrin that is elevated in lead exposure or iron deficiency anemia. Used interchangeably in this document with erythrocyte porphyrin, erythrocyte protoporthyrin, and free erythrocyte porphyrin or protoporthyrin.

APPENDIX B
PHYSICAL/CHEMICAL DATA FOR LEAD COMPOUNDS

B.1 DATA TABLES

TABLE B-1. PHYSICAL PROPERTIES OF INORGANIC LEAD COMPOUNDS[1]

					Solubility, g/100 ml		
Compound	Formula	M.W.	S.G.	M.P.	Cold water	Hot water	Other solvents
Lead	Pb	207.19	11.35	327.5	i	i	sa
Acetate	$Pb(C_2H_3O_2)_2$	325.28	3.25	280	44.3	221^{50}	s glyc
Azide	$Pb(N_3)_2$	291.23	—	expl.	0.023	0.09^{70}	—
Bromate	$Pb(BrO_3)_2 \cdot H_2O$	481.02	5.53	d180	1.38	sl s	—
Bromide	$PbBr_2$	367.01	6.66	373	0.8441	4.71^{100}	sa
Carbonate	$PbCO_3$	267.20	6.6	d315	0.00011	d	sa,alk
Carbonate, basic	$2PbCO_3 \cdot Pb(OH)_2$	775.60	6.14	d400	i	i	s HNO_3
Chloride	$PbCl_2$	278.10	5.85	501	0.99	3.34^{100}	i al
Chlorobromide	PbClBr	322.56	—	—	—	—	—
Chromate	$PbCrO_4$	323.18	6.12	844	6×10^{-6}	i	sa,alk
Chromate, basic	$PbCrO_4 \cdot PbO$	546.37	6.63	—	i	i	sa,alk
Cyamide	$Pb(CN)_2$	259.23	—	—	sl s	s	s KCN
Fluoride	PbF_2	245.19	8.24	855	0.064	—	s HNO_3
Fluorochloride	PbFCl	261.64	7.05	601	0.037	0.1081	—
Formate	$Pb(CHO)_2$	297.23	4.63	d190	1.6	20	i al
Hydride	PbH_2	209.21	—	d	—	—	—
Hydroxide	$Pb(OH)_2$	241.20	—	d145	0.0155	sl s	sa,alk
Iodate	$Pb(IO_3)_2$	557.00	6.155	d300	0.0012	0.003	s HNO_3
Iodide	PbI_2	461.00	6.16	402	0.063	0.41	s,alk
Nitrate	$Pb(NO_3)_2$	331.20	4.53	d470	37.65	127	s,alk
Nitrate, basic	$Pb(OH)(NO_3)$	286.20	5.93	d180	19.4	s	sa
Oxalate	PbC_2O_4	295.21	5.28	d300	0.00016	—	sa
Oxide	PbO	223.19	9.53	888	0.0017	—	s,alk
di Oxide	PbO_2	239.19	9.375	d290	i	i	sa
Oxide (red)	Pb_3O_4	685.57	9.1	d500	i	i	sa
Phosphate	$Pb_3(PO_4)_2$	811.51	7	1014	1.4×10^{-5}	i	s,alk
Sulfate	$PbSO_4$	303.25	6.2	1170	0.00425	0.0056	—
Sulfide	PbS	239.25	7.5	1114	8.6×10^{-5}	—	sa
Sulfite	$PbSO_3$	287.25	—	d	i	i	sa
Thiocyanate	$Pb(SCN)_2$	323.35	3.82	d190	0.05	0.2	s,alk

Abbreviations:
a - acid
al - alcohol
alk - alkali
d - decomposes
expl - explodes
glyc - glycol
i - insoluble
s - soluble
M.W. - molecular weight
S.G. - specific gravity
M.P. - melting point

TABLE B-2. TEMPERATURE VARIATION OF THE VAPOR PRESSURES OF COMMON LEAD COMPOUNDS[1]

Name	Formula	M.P.	Temperature °C 1 mm	10mm	40mm	100mm	400mm	760mm
Lead	Pb	327.4	973	1162	1309	1421	1630	1744
Lead bromide	$PbBr_2$	373	513	610	686	745	856	914
Lead chloride	$PbCl_2$	501	547	648	725	784	893	954
Lead flouride	PbF_2	855	solid	904	1003	1080	1219	1293
Lead iodide	PbI_2	402	479	571	644	701	807	872
Lead oxide	PbO	890	943	1085	1189	1265	1402	1472
Lead sulfide	PbS	1114	852 (solid)	975 (solid)	1048 (solid)	1108 (solid)	1221	1281

B.2. THE CHELATE EFFECT

The stability constants of chelated complexes are normally several orders of magnitude higher than those of comparable monodentate complexes; this effect is called the chelate effect and is very readily explained in terms of kinetic considerations. A comparison of the binding of a single bidentate ligand with that of two molecules of a chemically similar monodentate ligand shows that, for the monodentate case, the process can be represented by the equations:

$$\mathrm{M} + \mathrm{B} \xrightleftharpoons[k_b]{k_a} \mathrm{M\text{-}B} \qquad \text{(B-1)}$$

$$\mathrm{M\text{-}B} + \mathrm{B} \xrightleftharpoons[k_d]{k_c} \mathrm{MB_2} \qquad \text{(B-2)}$$

The related expressions for the bidentate case are:

$$\mathrm{M} + \mathrm{B\text{-}B} \xrightleftharpoons[k_2]{k_1} \mathrm{M\text{-}B\text{-}B} \qquad \text{(B-3)}$$

$$\mathrm{M\text{-}B\text{-}B} \xrightleftharpoons[k_4]{k_3} \mathrm{M}\!<\!\begin{matrix}\mathrm{B}\\ \mathrm{B}\end{matrix}\!\Big) \qquad \text{(B-4)}$$

The overall equilibrium constants, therefore, are:

$$K_1 = \frac{k_a k_c}{k_b k_d};\ K_2 = \frac{k_1 k_3}{k_2 k_4}$$

For a given metal, M, and two ligands, B and B-B, which are chemically similar, it is established that k_1 and k_a have values similar to each other, as do k_2 and k_b, k_4 and k_d; each of these pairs of terms represents chemically similar processes. The origin of the chelate effect lies in the very large value of k_3 relative to that of k_c. This comes about because k_3 represents a unimolecular process, whereas k_c is a bimolecular rate constant. Consequently, $K_2 >> K_1$.

This concept can, of course, be extended to polydentate ligands; in general, the more extensive the chelation, the more stable the metal complex. Hence, one would anticipate, correctly, that polydentate chelating agents such as penicillamine or EDTA can form extremely stable complexes with metal ions.

B.3 REFERENCES FOR APPENDIX B

1. Handbook of Chemistry and Physics, 56th Ed. R.C. Weast (ed.). Cleveland, The Chemical Rubber Co. 1975.
2. Stull, D.R. Vapor pressure of pure substances: Organic compounds. Ind. Eng. Chem. *39*(4):517-540, 1947.

APPENDIX C
ADDITIONAL STUDIES OF ENVIRONMENTAL CONCENTRATIONS OF LEAD

This collection of studies is intended to extend and detail the general picture of lead concentrations in the environment and in proximity to identified major sources as portrayed in Chapter 7. The list is by no means all-inclusive, but is intended to be representative and to supplement the data cited in Chapter 7.

C.1 GENERAL AMBIENT AIR CONCENTRATIONS

C.1.1 Seven-City Study

A special lead study (Seven-City Study) was conducted for 12-month periods between 1968 and 1971 in Cincinnati, Los Angeles, Philadelphia, Houston, New York City, Washington, D.C., and Chicago. Samples of ambient air were analyzed by atomic absorption spectroscopy. The monthly average lead concentrations obtained are summarized in Table C-1.

This study, specifically designed to measure ambient lead concentrations at a variety of sites within each of the cities, incorporated techniques that would provide the most precise measure of ambient lead concentrations available. A membrane filter was used instead of a glass filter, and the samples were collected continuously over 2 to 3 days rather than collected in biweekly 24-hr periods as in the NASN. The high annual average lead concentrations found in the Los Angeles area are largely attributable to heavy automotive emissions.

C.1.2 Birmingham, Alabama

During 1964 and 1965, seasonal levels of trace metals were determined from suspended particulate samples collected at 10 area sampling sites at Birmingham, Alabama, as a part of the Alabama Respiratory Disease and Air Pollution Study initiated in 1962. This monitoring study produced data representative of area source industrial pollution. Samples from each of the 10 sites were composited on a seasonal basis to give a total of 40 pooled samples. The lead data are summarized in Table C-2. The maximum seasonal lead concentration (3.5 $\mu g/m^3$) occurred at Birmingham site 4 during the winter. Only 2 sites showed average concentrations $> 2\ \mu g/m^3$ for the year, Birmingham site 4 (3.0 $\mu g/m^3$) and Tarrant (2.3 $\mu g/m^3$). These results are typical for a medium-sized industrialized urban area.

C.1.3 Kanawha Valley, West Virginia[3]

A comprehensive air pollution study was conducted in the Kanawha River Valley in the vicinity of Charleston, West Virginia (Figure C-1), during 1964 and 1965. Twenty-four-hour samples of suspended particulate matter were collected at 14 strategically located sites. Samples from selected sites were composited on a seasonal basis (fall 1964, winter 1964 and 1965, and summer 1965) and the composites were analyzed for trace-metal content by the NASN emission spectrographic procedure. The data for lead are presented in Table C-3. Highest concentrations of suspended lead were found during the fall of 1964 at the St. Albans, Kanawha City, and Charleston sites.

Lead in dustfall measurements (settled particulates) for the same stations are also presented in Table C-3. The dustfall was collected by exposing wide-mouth jars for a period of 1 month; then composite samples were analyzed. The highest average concentrations of settled lead occurred at the Smithers site (11.2 mg/m^2-mo), and at the South Charleston-East site (11.6 mg/m^2-mo).

The combustion of solid fuels (coal and coke) is the primary source of lead emissions in the Kanawha Valley. Additional sources are metallurgical operations, asphalt hot-mix production, and other industrial processes. In most cases, these sources have inadequate air pollution control equipment. The lead concentrations found are somewhat low when

TABLE C-1. SUMMARY OF MONTHLY AVERAGE LEAD CONCENTRATIONS FOUND IN SEVEN-CITY STUDY[1]

City	Site type[a]	Months of data	Monthly concentration, $\mu g/m^3$		
			Min.	Max.	Avg.
Los Angeles	C	12	2.4	5.8	4.2
	C	12	2.6	6.8	4.5
	R	12	2.1	5.0	3.6
	R	12	2.7	5.4	3.8
	R	12	2.1	4.4	3.1
	R	12	1.4	3.9	2.5
	I	12	1.7	7.0	3.7
	C	12	2.5	7.6	4.8
Philadelphia	M	12	1.3	2.7	1.9
	C	12	1.2	2.6	1.8
	C	12	2.6	5.1	3.8
	I	12	1.5	3.0	2.2
	R	12	0.9	2.0	1.4
	M	12	0.6	1.7	1.1
	R	12	0.6	1.5	1.1
	R	12	1.1	2.6	1.7
	R	12	0.8	1.7	1.3
	R	12	0.7	1.6	1.0
Cincinnati	C	12	1.3	3.1	2.0
	R	12	0.8	2.6	1.5
	I	12	1.2	2.8	2.2
	P	12	0.5	1.2	0.9
	F	12	0.1	0.5	0.3
	F	12	0.2	0.5	0.3
Los Alamos	R	12	0.1	0.3	0.2
	C	12	0.1	0.3	0.2
Houston	R	12	0.7	2.7	1.2
	C	12	0.7	1.9	1.1
	C	12	1.2	3.2	2.2
	C	12	1.5	4.1	2.4
	M	12	1.0	2.2	1.3
	R	12	0.6	1.4	0.9
	R	12	0.6	1.2	0.8
Chicago	R	12	1.0	1.7	1.3
	M	12	1.1	1.7	1.4
	R	12	1.0	2.1	1.6
	M	12	1.3	2.2	1.8
	C	12	1.4	2.3	1.9
	R	12	1.2	2.2	1.6
	R	7	0.9	2.7	1.3
	M	12	1.1	2.1	1.6
	R	12	1.2	3.5	2.0
Washington, D.C.	R	12	0.7	1.6	1.1
	C	7	1.2	2.2	1.7
	C	12	1.6	3.9	2.3
	R	12	1.4	2.8	1.8
	R	12	1.0	1.7	1.2
	F	12	0.9	1.6	1.1
	R	12	1.8	3.5	2.4
	R	12	0.8	1.8	1.1
New York	M	11	1.1	2.9	1.7
	M	12	1.4	2.6	2.1
	R	12	1.4	2.1	1.7
	R	12	1.3	2.2	1.7
	M	12	1.2	2.7	2.1
	R	12	0.8	1.9	1.4
	R	12	0.9	1.6	1.2
	R	12	0.9	1.4	1.2
	R	12	0.8	1.4	1.1

[a] C - commercial; I - industrial; R - residential; M - mixed; F - farm; and P - park.

TABLE C-2. SEASONAL LEAD CONCENTRATIONS IN BIRMINGHAM, ALABAMA, AREA, 1964-1965 ($\mu g/m^3$)

Place	Site	Seasonal average concentrations				Study period average concentration
		Spring	Summer	Fall	Winter	
Bessemer	1	0.9	0.7	1.1	0.6	0.8
Birmingham	3	0.7	1.4	1.7	1.4	1.3
Birmingham	4	3.2	2.8	2.3	3.5	3.0
Birmingham	5	1.2	1.6	1.8	0.8	1.4
Birmingham	7	1.2	1.4	1.3	1.8	1.4
Fairfield	1	0.6	0.5	0.6	0.3	0.5
Irondale	1	0.6	0.4	0.9	0.6	0.6
Mt. Brook	1	0.5	0.6	1.0	0.5	0.6
Tarrant	1	1.1	1.8	3.0	3.4	2.3
Vestavia	1	0.8	0.8	0.5	0.7	0.7

one considers the diversity of industrial activity and the meteorological and topographic characteristics prevailing. The highest values found were associated with sampling sites adjacent to major traffic arteries, which demonstrates the contribution from mobile sources.

C.1.4 Study of Lead Deposition in 77 Cities[4]

Settled particulates were collected in 77 mid-western cities from September through December 1968. Within each city, sites were chosen to represent residential, commercial, and industrial areas. The lead content of the settled particulates was determined by atomic absorption spectrophotometry, and the depositions were expressed as mg/m^2-mo. The highest amounts found in residential, commercial, and industrial areas were in South Bend, Indiana (80 mg/m^2-mo in November); Nashville, Tennessee (346 mg/m^2-mo in October); and Omaha, Nebraska (137 mg/m^2-mo in November); respectively. Maximum readings by month occurred in Muncie, Indiana (industrial) (105 mg/m^2-mo in September); Nashville, Tennessee (commercial) (346 mg/m^2-mo in October); Omaha, Nebraska (industrial) (137 mg/m^2-mo in November); and Waterloo, Iowa (industrial) (94 mg/m^2-mo in December). The data are summarized in Table C-4.

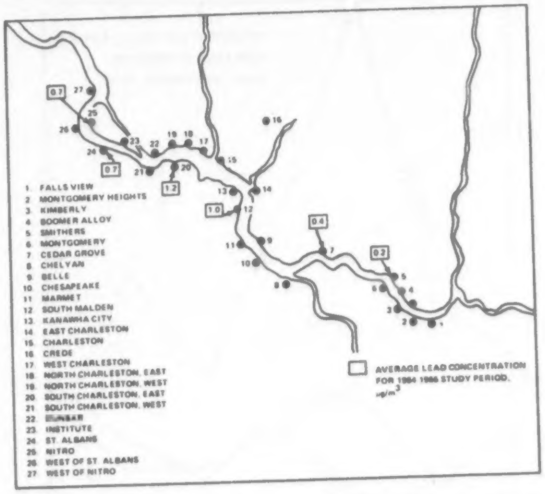
C.2 SOURCE-ORIENTED AMBIENT AIR CONCENTRATIONS

C.2.1 Southern Solano County, California[5]

The State of California Air Resources Board coordinated a joint study, conducted by several state agencies between March 1970 and November 1971, to determine the cause of death of a number of horses in the Benicia area from 1968 to 1970. Figure C-2 is a map of this area showing sampling site locations. The evidence strongly suggested that the

TABLE C-3. LEAD DATA FROM KANAWHA VALLEY STUDY[3]

Sampling sites, location and no.	Lead in suspended particulates, μg/m³					Lead in settled particulates, mg/m²/mo, study period average
	Fall 1964	Winter 1964-1965	Spring 1965	Summer 1965	Study period average	
Falls View (1)	—	0.2	—	—	—	—
Smithers (5)	0.4	0.3	0.3	0.0	0.2	11.2
Montgomery (6)	—	0.6	—	—	—	6.7
Cedar Grove (7)	0.5	0.4	0.2	0.4	0.4	4.8
Marmet (11)	—	0.5	—	—	—	3.8
Kanawha City (13)	2.1	0.8	0.6	0.5	1.0	2.8
Charleston (15)	—	0.9	—	—	—	—
West Charleston (17)	—	0.7	—	—	—	—
North Charleston-W (19)	—	0.7	—	—	—	8.6
South Charleston-E (20)	2.7	0.6	0.6	1.0	1.2	11.6
Dunbar (22)	—	0.4	—	—	—	—
St. Albans (24)	1.3	0.9	0.3	0.4	0.7	3.0
Nitro (25)	1.0	1.4	0.2	0.3	0.7	3.4
Nitro-West (27)	—	0.1	—	—	—	—


0.7
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3
2
1
1. FALLS VIEW
2 MONTGOMERY HEIGHTS
3 KIMBERLY
4 BOOMER ALLOY
5 SMITHERS
6 MONTGOMERY
7 CEDAR GROVE
8 CHELYAN
9 BELLE
10 CHESAPEAKE
11 MARMET
12 SOUTH MALDEN
13 KANAWHA CITY
14 EAST CHARLESTON
15 CHARLESTON
16 CREDE
17 WEST CHARLESTON
18 NORTH CHARLESTON, EAST
19 NORTH CHARLESTON, WEST
20 SOUTH CHARLESTON, EAST
21 SOUTH CHARLESTON, WEST
22 DUNBAR
23 INSTITUTE
24 ST. ALBANS
25 NITRO
26 WEST OF ST. ALBANS
27 WEST OF NITRO
AVERAGE LEAD CONCENTRATION FOR 1964 1966 STUDY PERIOD, μg/m³

Figure C-1. Locations of fixed sampling stations in Kanawha River Valley.[3]

TABLE C-4. DATA ON LEAD DEPOSITION IN 77 MIDWESTERN CITIES[4] (mg/m²/mo)

Lead deposition		Lead deposition	
Area	Concentration, geometric mean	Month	Concentration, geometric mean
Residential	5.24	September	9.11
Commercial	9.80	October	8.71
Industrial	12.78	November	9.15
		December	8.06

horses died of lead poisoning that was caused by ingestion of lead deposited on pasture grass from a smelter plant at Selby, California. The ambient air concentrations of particulate lead were typical of those found in urban and suburban areas. It was concluded that horses in this area should not be allowed to subsist on pasture grass alone, but should receive supplemental feed. Tables C-5 and C-6 contain the data on suspended and deposited lead obtained during the study. Note that the fallout rates are on a daily basis.

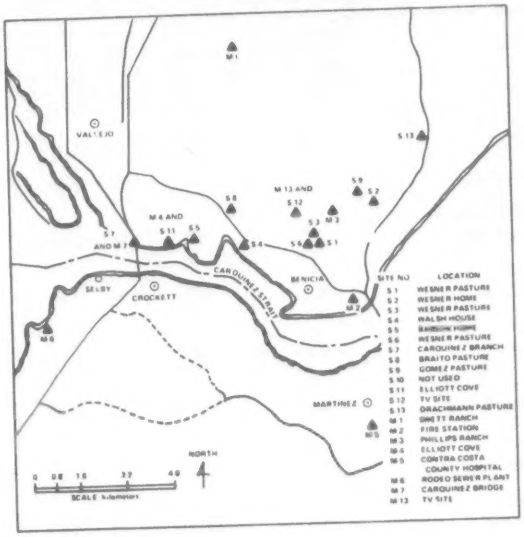
M 1
VALLEJO
S 13
S 9
S 2
M 13 AND
S 12
S 8
M 3
M 4 AND
S 3
S 7
AND M 7
S 11
S 5
S 4
S 6
S 1
CARQUINEZ STRAIT
BENICIA
SELBY
CROCKETT
M 2
M 6
MARTINEZ
M 5
NORTH
0 0.8 1.6 3.2 4.8
SCALE kilometers
SITE NO LOCATION
S 1 WESNER PASTURE
S 2 WESNER HOME
S 3 WESNER PASTURE
S 4 WALSH HOUSE
S 5
S 6 WESNER PASTURE
S 7 CARQUINEZ BRANCH
S 8 BRAITO PASTURE
S 9 GOMEZ PASTURE
S 10 NOT USED
S 11 ELLIOTT COVE
S 12 TV SITE
S 13 DRACHMANN PASTURE
M 1 SWETT RANCH
M 2 FIRE STATION
M 3 PHILLIPS RANCH
M 4 ELLIOTT COVE
M 5 CONTRA COSTA COUNTY HOSPITAL
M 6 RODEO SEWER PLANT
M 7 CARQUINEZ BRIDGE
M 13 TV SITE

Figure C-2. Air sampling sites for Southern Solano County, California, study.[5]

C.2.2 Omaha, Nebraska[6]

In April and May of 1968, a study of settled lead by the EPA Division of Health Effects Research showed central Omaha, Nebraska, to have the highest concentrations of deposited lead of 22 midwestern cities. Because automobile emissions should reflect the relatively low population density, the possibility of a significant contribution to air lead

TABLE C-5. LEAD CONCENTRATIONS IN AIR DETERMINED BY ANALYSIS OF SUSPENDED PARTICULATE, SOUTHERN SOLANO COUNTY, CALIFORNIA, MARCH-MAY 1970[5]

Site	Distance from Selby,[a] km	Lead concentrations, $\mu g/m^3$		
		High	Low	Mean
Carquinez Bridge	1.9	8.45	0.35	3.49
Elliot Cove	3.0	0.93	0.27	0.52
Babson house	3.7	0.82	0.58	0.70
Braito dump	5.6	0.69	0.07	0.64
Walsh house	5.7	0.62	0.14	0.40
Braito TV transmitter site	7.7	1.07	0.25	0.59
Wesner pasture	7.8	0.56	0.40	0.42
Wesner pasture	8.0	0.66	0.11	0.38
Wesner pasture	8.3	0.51	0.03	0.27
Gomez pasture	10.0	0.28	0.03	0.11
Wesner house	10.2	0.22	0.02	0.14
San Francisco[b]	22.0	3.50	1.15	2.12
Fremont[b]	20.0	2.24	0.59	1.04
San Rafael[b]	19.2	2.04	0.41	1.14

[a] Location of suspected lead emissions source. See text.

[b] 1969 data provided by Bay Area Air Pollution Control District.

TABLE C-6. TOTAL LEAD AND LEAD FALLOUT DETERMINED BY ANALYSIS OF DUSTFALL SAMPLES, SOUTHERN SOLANO COUNTY, CALIFORNIA, JUNE-SEPTEMBER 1970[5]

Site	Distance from Selby,[a] km	Sample period, days	Total solids, mg	Total lead, μg	Lead fallout, mg/m^2-day
Carquinez Bridge	1.9	30	49.2	1435	2.78
Braito dump	5.6	30	58.7	195	0.38
Braito TV transmitter site	7.7	60	101.7	520	0.50
Wesner pasture	8.0	31	370	185	0.35
Wesner pasture	8.0	31	162	155	0.29
Wesner pasture	8.0	31	171.4	195	0.37
Wesner pasture	8.0	31	109.8	255	0.48
Wesner pasture	8.0	31	351.7	210	0.39
Wesner pasture	8.0	31	220.2	4535	8.51
Wesner pasture	8.0	30	83.5	430	0.83
Wesner pasture	8.3	30	163.6	705	1.37
Gomez pasture	10.0	32	45.0	150	0.27
Drachman pasture	13.4	30	26.5	75	0.15

[a] Location of suspected lead emissions source. See text.

from other sources (two battery plants, one refinery) in the central city area was considered. Consequently, from May to November 1970, monitoring of air lead in Omaha was conducted at five sites: one industrial (I), one commercial (C), one mixed (M), and two residential (R). All samples were taken at 15-ft elevation, and all data were reported as the composited averages of 24-hr samples collected 3 times weekly. The monthly composite average of air lead concentrations at the sampling sites is shown in Figure C-3. Air lead levels in central Omaha at sites C and I were not only comparable with those of similar sites in Chicago, New York City, and Houston from the same months, as reported by EPA, but the maximum monthly mean at the industrial site (in July) exceeded the maximum monthly mean of all sites in these other cities.

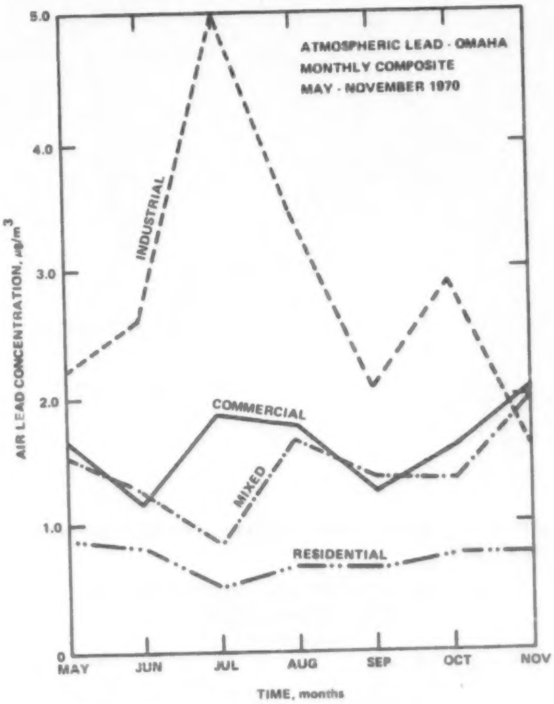

Figure C-3. Omaha, Nebraska study: mean monthly composite atmospheric lead at industrial, commercial, mixed, and two residential sites. Mean is that of representative 24-hour samples collected three times weekly. The autumnal peak at all but the industrial site parallels the usual Omaha pattern for particulates.[6]

C.2.3 El Paso, Texas[7,8]

The El Paso, Texas, study was initiated in 1971 as a result of the discovery of increased lead deposition in the vicinity of a local smelter whose emissions rose from 256 MT in 1969 to 463 MT in 1970. The El Paso City-County Health Department then began special ambient air and soil sampling in addition to routine operation of their nine-station particulate sampling network. Particulate samples were collected with high-volume samplers over 24-hr periods and were then analyzed for lead by atomic absorption spectroscopy. The results for 1971 from the nine-station network are given in Table C-7. Daily sampling at 6 selected sites in Smeltertown was continued beginning in February 1972. Daily lead concentrations at four ground level sites ranged from 0.49 to 75 $\mu g/m^3$ and averaged 6.6 $\mu g/m^3$ over 86 days. Average concentrations of 3.6 and 6.5 $\mu g/m^3$ were found at 2 rooftop sites.

TABLE C-7. LEAD CONCENTRATIONS IN SUSPENDED PARTICULATE AIR SAMPLES FROM EL PASO, TEXAS, 1971[7]

Location	Distance from smelter, km	No. of samples	Suspended atmospheric lead concentration, $\mu g/m^3$	
			Range	Average
Airport	12.8 E	84	0.38 to 5.82	0.96
Northeast	16 NE	73	0.12 to 3.68	0.76
Canutillo	15.2 NW	45	0.10 to 1.50	0.46
Shorty Way	8 NW	75	0.18 to 4.51	1.03
Tillman	4.8 SE	70	0.02 to 22.16	2.69
Ysleta	21.6 SE	71	0.18 to 4.81	1.39
Coronado	4.8 N	94	0.08 to 8.62	0.83
Kern	2.4E	26	0.12 to 7.28	2.72
Executive	1.6 NE	65	0.26 to 6.67	1.16

C.2.4 Helena Valley, Montana[9]

During the summer and fall of 1969, a source-oriented study of the Helena Valley, Montana, area (Figure C-4) was undertaken using dustfall bucket and high-volume sampling techniques. During this period, Helena residents were exposed to an average daily lead concentration of 0.1 $\mu g/m^3$, with maximum concentrations of up to 0.7 $\mu g/m^3$. The residents of the East Helena area were exposed to an average daily concentration of 0.4 to 4.0 $\mu g/m^3$, depending upon proximity to the source, with maximum daily exposures of up to 15 $\mu g/m^3$. Within a 1-mile radius of the East Helena smelter, settled particulate lead values ranged from 30 to 108 $mg/m^2/mo$. Table C-8 summarizes the dustfall and suspended particulate data acquired during this study, and Figure C-4 shows the deposition of lead (dustfall) in the area.

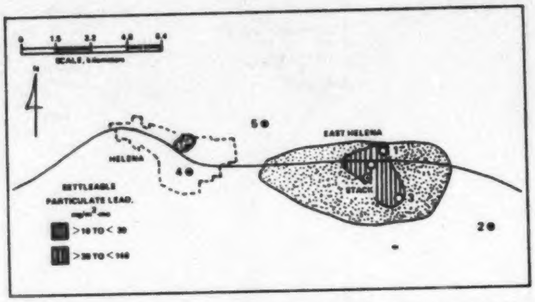

Figure C-4. Settleable particulate lead radial distribution from Helena Valley environmental pollution study.[9]

C.2.5 Southeast Missouri[10]

Studies were carried out in 1971 in the Viburnum Trend or New Lead Belt in southeast Missouri to determine the magnitude and distribution of atmospheric pollutants from lead mining and smelting operations. This industrial district has become one of the world's largest lead-producing areas by mining more than 392,277 MT of lead, or 75 percent of the entire U.S. lead production, during 1970. Settleable particulates were collected monthly at 10 locations in western Iron County shown in Figure C-5. Annual averages for each site are included in the figure; monthly maximum values are listed in Table C-9. Annual averages for suspended lead collected in Glover, Mo. (Site 43, southeastern Iron County), by high-volume sampler were 3.4 $\mu g/m^3$ (20 samples) in 1970, 5.3 $\mu g/m^3$ (32 samples) in 1971, and 5.6 $\mu g/m^3$ (28 samples) in 1972.

TABLE C-8. PARTICULATE DATA SUMMARY FROM HELENA VALLEY, MONT., ENVIRONMENTAL POLLUTION STUDY[9]

Station	Location[a]	Settleable particulate lead, $mg/m^2/mo$					Suspended particulate lead in glass fiber filter sample, $\mu g/m^3$			
		Jun.	Jul.	Aug.	Sept.	Oct.	No. samples	Max.	Min.	Average
1	0.8 mi; 34°	3	19	10	19	40	76	5.3	< md[b]	0.45
2	2.5 mi; 105°	1	4	3	9	10	87	2.5	< md	0.24
3	0.4 mi; 112°	54	106	5	63	108	85	16.0	< md	1.25
4	4.5 mi; 274°	1	4	3	7	7	82	7.0	< md	0.10
6	0.5 mi; 2°	—	—	—	27	60	34	15.0	0.2	3.89

[a] Distance and compass direction from smelter stack.

[b] Minimum detectable.

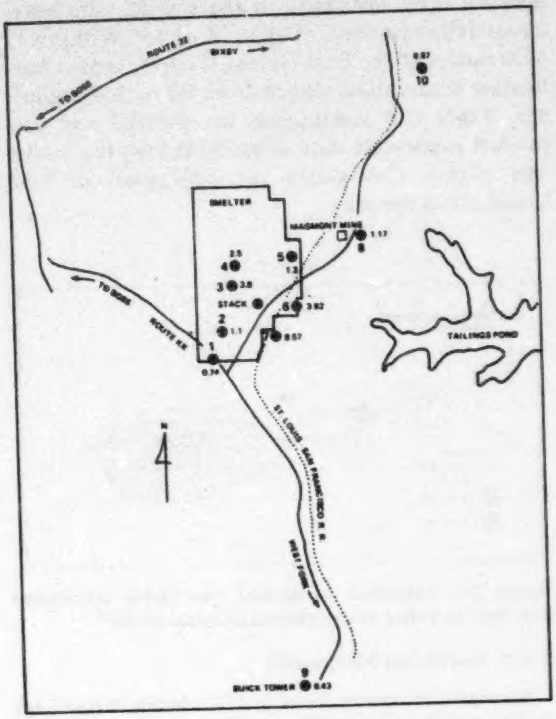

Figure C-5. Annual average of settleable particulate lead at sites near Missouri lead mine and smelter, g/m²/mo.[10]

C.2.6 Helsinki, Finland[11]

Investigators for the Agricultural Research Center in Tikkurila, Finland, an industrial and residential area near Helsinki, found high lead levels in soil. To clarify the origin of this excess lead, the Institute of Occupational Health conducted a dustfall lead survey in the area. Eighty collectors were located over a 40-km² area for a period of 1 month, October 6 to November 7, 1970. Individual ashed samples were analyzed by emission spectrography and the water-soluble fractions were analyzed by atomic absorption spectroscopy.

The highest lead deposition values in Helsinki were observed in areas with heavy traffic and ranged from 10 to 20 mg/m²/mo as compared to 0 to 4 mg/m²/mo in predominantly housing and residential areas.

In the Tikkurila area, industrial contributions increased deposited lead values fortyfold in some areas. The deposited lead values ranged from background in outlying areas to as high as 200 mg/m²/mo near a lead smelter, with most of the values below 100 mg/m²/mo.

C.2.7 Meza River Valley, Yugoslavia[12]

In 1967, work was initiated in the community of Zerjav, situated in the Slovenian Alps on the Meza River, to investigate contamination by lead of the air, water, snow, soil, vegetation, and animal life, as well as the human population. The smelter in this community produces about 19,954 MT of lead annually; until 1969 the stack emitted lead oxides without control by filters or other devices. Five sampling sites with high-volume samplers operating on a 24-hr basis were established in the four principal settlements within the Meza River Valley (Figure C-6): (1) Zerjav, in the center, the site of the smelter, housing 1503 inhabitants; (2) Rudarjevo, about 2 km to the south of Zerjav with a population of 100; (3) Crna, some 5 km to the southwest, population 2198, where there are two sites (Crna-SE and Crna-W); and (4) Mezica, a village about 10 km to the northwest of the smelter with 2515 inhabitants. The data in Table C-10 are sufficient to depict general environmental contamination of striking proportions.

TABLE C-9. PEAK DEPOSITION RATES OF LEAD MEASURED IN SOUTHEAST MISSOURI[10]

1971	Station no.	Wind direction	Distance, m	Lead deposition rate, mg/m²/mo	Wind frequency, % prevailing direction
May-June	6	E	81	5.88	18(S), 12(WNW)
July	7	SSE	91	5.54	14(SSE), 13(S), 10(SSW)
August	10	NE	633	4.57	14(SSE), 11(S), 10(SSW)
September	7	SSE	91	7.76	22(S), 12(SSE), 12(SSW)
October	7	SSE	91	5.10	10(N), 10(W), 10(SE), 11 (ESE)
November	3	WNW	61	2.01	26(S), 12(SSW), 10(WSW), 8(SSE)

C.2.8 Ontario, Canada[13]

Studies of lead concentrations in soils, vegetation, and the ambient air were conducted in the vicinity of a secondary smelter and a battery manufacturing plant in a large urban area in southern Ontario. For comparative purposes, data were also collected in a similar control neighborhood that had no such industrial sources. Emissions of lead from the smelter were estimated to be 17 tons per year; from the battery plant, 6 tons per year. Averages and ranges of

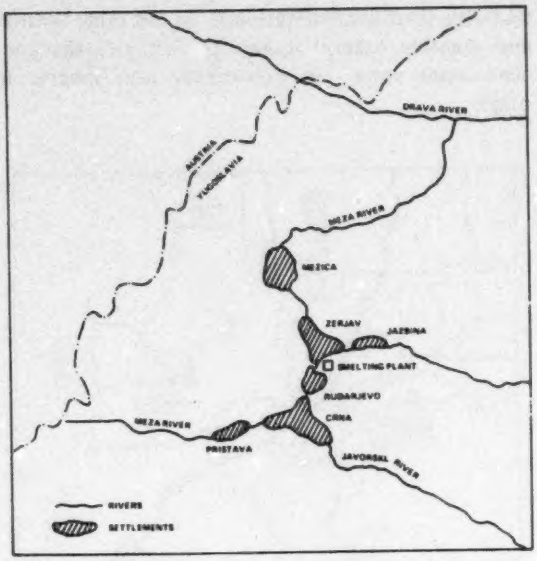

Figure C-6. Schematic plan of lead mine and smelter from Meza Valley, Yugoslavia, study.[12]

TABLE C-10. ATMOSPHERIC LEAD CONCENTRATIONS (24-hr) IN THE MEZA VALLEY, YUGOSLAVIA, NOVEMBER 1971 TO AUGUST 1972[12]

Site	Pb concentration μg/m^3		
	Minimum	Maximum	Average
Mezica	0.1	236.0	24.2
Zerjav	0.3	216.5	29.5
Rudarjevo	0.5	328.0	38.4
Crna SE	0.1	258.5	33.7
Crna W	0.1	222.0	28.4

lead concentrations are summarized in Table C-11. Both soil and foliage samples showed definite trends toward reduced concentrations with increasing distance from the industrial sources.

C.3 CONCENTRATIONS OF LEAD IN SOILS AND URBAN DUSTS

As mentioned in Chapter 5, surficial materials in the continental United States contain an average of about 15 ppm of lead; 94 percent of the measurements showed 30 ppm or less. Higher concentrations are encountered in the vicinity of lead ore deposits and, of course, in the proximity of human activities involving lead. Soils apparently receive lead in the amounts of about 1 μg/cm^2/yr from precipitation and 0.2 μg/cm^2/yr from dustfall[14] in areas remote from intensive human activity. These small additions to the lead content of the soil are not detectable by ordinary means because they add only about 0.2 percent to the total lead in the top 6 in of the soil. Lead levels are higher in surface soils than in deeper layers. Swain and Mitchell[15] studied lead profiles in 8 soil types in Scotland and showed that the lead content at 115 cm (45 in) averaged one-half that at the surface. The reduction of concentration with depth is also substantiated by the findings of others. Goldschmidt[16] proposed the theory that lead is concentrated in the humus or organic fraction of soils in forests because it is taken up slowly by tree roots and transported to the leaves, which fall and decay. Tyler[17] points out that a passive ion exchange favors an accumulation of lead and other heavy metals in dead organic matter, litter, and humus. He also states that most plant material subjected to decomposition usually shows an increase in the concentration of lead, cadmium, nickel, iron, copper, etc., calculated on dry weight.

The use of leaded gasolines has produced elevated soil lead levels adjacent to most streets and roadways. This phenomenon was first observed as early as 1933 in England,[18] and has been intensively

TABLE C-11. COMPARISON OF LEAD LEVELS IN THE SURROUNDINGS OF TWO LEAD INDUSTRY FACILITIES AND AN URBAN CONTROL AREA[13]

Industry or area	Soil, ppm (0.5 cm depth)	Tree foliage ppm		Air, μg/m^3 (24-hour samples)
		Unwashed	Washed	
Secondary smelter				
Mean	2.615	250	187	3.87[a]
Range	133 to 21.200	38 to 3.530	27 to 2.740	Max: 74.4
Battery plant				
Mean	1.996	149	76	2.21[b]
Range	95 to 17.300	34 to 459	16 to 387	Max: 31.0
Urban control area				
Mean	482	73	43	1.02[c]
Range	18 to 1.450	15 to 253	10 to 124	Max: 4.0

[a] April 1973 to May 1974.
[b] November 1973 to May 1974.
[c] January 1974 to April 1974.

studied in recent years.[19] An example of this phenomenon is taken from a study of the Saline Branch watershed, which includes Champaign, Illinois. One facet of this comprehensive study[20] consisted of analyses for lead in soil at increasing distances from a low-traffic-volume street (400 vehicles/day) and a high-traffic-volume street (14,000 vehicles/day). As shown on curve A in Figure C-7, lead concentrations stabilized at about 20 ppm beyond 15 meters from the low-volume street and rose slightly near the house. Unfortunately, the exterior construction of the house is not described. As curve B in Figure C-7 shows, lead concentrations of about 1800 ppm in the soil adjacent to the high-volume street are 9 times higher than in soil adjacent to the low-volume street; the concentration drops rapidly to a minimum of 30 ppm a little more than 20 m from the street and then rises again abruptly near the house to 90 ppm. This house is described as brick and unguttered. Although some leaching of lead from painted trim may be involved, the increase near the house is believed attributable chiefly to lead particles in traffic dust washed from the unguttered roof by rain and deposited in the soil next to the house.

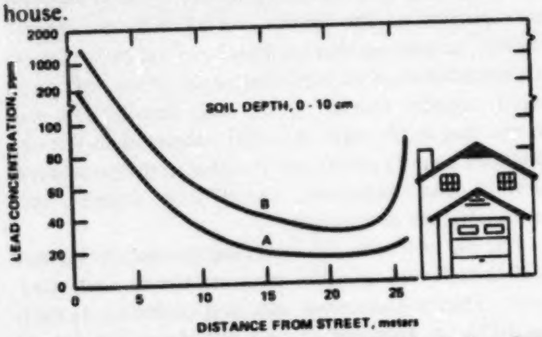

Figure C-7. Soil transects by two streets: Curve A = low-traffic-volume (400 veh/day); Curve B = high-traffic-volume (14,000 veh/day).[20]

Soil lead levels in the vicinity of stationary sources of lead emissions are often very high, and, unlike the rapid drop-off near highways, very extensive. This is particularly true for old installations. Figure C-8 shows levels recently found near an old smelter in El Paso, Texas.[21] Similar data, compiled from a 3-year-old Russian lead smelter,[22] are shown in Table C-12. The concentration decrease with both depth and distance is also apparent here. Information on soluble lead levels in soil near a similar complex in Great Britian is presented in a report by Little and Martin.[23] Barltrop reported values up to 30,000 μg/g in villages in the eastern half of Derbyshire County, England.[24] In this instance, the soil included lead contamination from old mine tailings and possible natural mineralization, i.e., the concentrations were not exclusively atmospheric in origin.

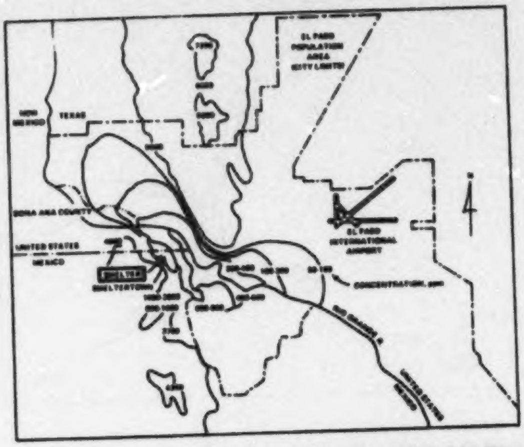

Figure C-8. Surface soil levels (ppm) of lead in El Paso, Texas, and Dona Ana County, New Mexico, 1972.[21]

TABLE C-12. LEAD CONTENT OF SOIL NEAR 3-YEAR-OLD RUSSIAN SMELTER, E. KAZAKHSTAN (mg/100 g air-dried soil)[a]

Distance from source, m	Surface layer	Soil depth	
		25 cm	75 to 100 cm
500	23.9711	4.1747	0.0748
1.000	9.0163	1.8368	—
2.000	1.4207	0.7432	0.0545
3.000	1.2192	0.5991	0.0474
5.000	0.1031	0.0649	0.0233
16.000	0.0943	0.0778	0.0292

[a] Multiplying by 10 yields ppm.

Table C-13, derived from studies done in 1959 and 1960,[25] gives lead levels of soil adjacent to another Russian lead smelter. The plant is located in a valley surrounded by mountains that hinder natural ventilation. In addition, plant emissions are inadequately controlled. Methods of sample preparation and analysis of the soil samples are not given, however; nor is it stated whether the soil weights used were for dried or undried material.

Paluch and Karweta[26] reported observations on soil lead near a new lead-zinc primary smelter in Poland. Soil analyses were made in several areas prior to operation of the factory and after 1 year of operation. Samples were extracted with hot concentrated hydrochloric acid and analyzed for lead content by the dithizone method. Levels found are given in milligrams of lead per kilogram of dried soil. Values

TABLE C-13. LEAD CONTENT OF SOIL IN VICINITY OF RUSSIAN LEAD PLANT IN KAZAKHSTAN[36]

Distance from source km	Number of samples	Lead content of soil, mg/100 g[a]					
		0 to 1 cm depth			25 cm depth		
		Maximum	Minimum	Average	Maximum	Minimum	Average
On grounds	12	11.170.0	1.300.0	5.546.0	6.800.0	510.0	3.143.0
0.5	10	2.420.0	470.0	1.156.0	650.0	130.0	456.0
1.0	20	1.170.0	130.0	613.0	990.0	200.0	430.0
1.5	6	720.0	170.0	369.0	720.0	70.0	340.0
2.0	6	1.070.0	250.0	530.0	610.0	70.0	260.0
3.0	4	340.0	130.0	235.0	260.0	100.0	180.0
5.0	4	97.0	80.0	88.5	46.0	40.0	43.0
40.0	4	3.0	2.5	2.7	Trace	Trace	Trace

[a] Multiplying by 10 yields ppm.

given are the average of three samples. Two sites are of particular interest, a woods of young pines 2 km from the smelter and a tree nursery at 3 km. Before and after lead levels in the top 5 cm of soil at these locations were 39 and 89 mg/kg for the former, and 54 and 81 mg/kg for the latter. At other sampling sites the data were quite variable, but these were agricultural lands subject to cultivation, to fertilization, or to both. The wooded sites were not disturbed in this manner.

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APPENDIX D

UNITS AND METRIC CONVERSION FACTORS

In each of the disciplines dealing with lead in a sector of the environment, conventions for units have evolved that are convenient to each but not always familiarly translatable from one to the other, even when expressed in metric units. There are also two distinct categories of measurements: concentrations and transfer rates. Within each category of measurements, straightforward conversion factors translate the quantities from one system of units to another. Connections between the two categories are bridged only by mathematical models of varying complexity that account for all significant transfer rates, both into and out of a given context, as well as measure that context's capacity to distribute and equilibrate any net change that will add to or substract from its initial concentration.

D.1 CONCENTRATIONS

Airborne lead concentrations are customarily reported in units of mass per volume: micrograms of lead per cubic meter of air ($\mu g/m^3$). Concentrations of lead in soils and dusts are reported in units of mass per mass: micrograms of lead per gram of the parent material ($\mu g/g$), or as parts per million (ppm). When ppm refers to mass, the expression is interchangeable with $\mu g/g$.

Concentrations of lead in water (dissolved or suspended) may be reported in parts per billion (ppb) or micrograms per liter (μg/liter). For our purposes, a liter of water can be equated with 1000 g, and units of μg/liter can be interchanged with ppb or nanograms per gram (ng/g).

Concentrations of lead in food are usually given in parts per million (ppm), micrograms per gram ($\mu g/g$), or milligrams per kilogram (mg/kg), all of which are interchangeable.

Concentrations of lead in blood may be reported in micrograms per deciliter ($\mu g/dl$) or in micrograms per 100 grams ($\mu g/100$ g). These are not equivalent since 1 dl of blood weighs between 105 and 106 g.

D.2 TRANSFER RATES

In general, transfer rates describe the movement of material from one medium or context to another in units of mass per time or mass per quantity (mass or volume) of a parent material. Some rates include a linear or area dimension to express the transfer per unit of interface between media.

The lead in ores that is transfered to smelters and hence to manufactured products is described by production figures and reported in tons (short) per year (tons/yr) or tonnes (metric) per year (MT/yr). The attendant dispersal of some of that lead into the air, water, and soil is described by emission factors: tons per year (tons/yr), kilograms per day (kg/day), pounds per ton of raw material or product (lb/ton), pounds per thousand gallons ($lb/10^3$ gal), grams per kilometer (g/km), etc.

The most familiar transfer rate between media is perhaps the dustfall or deposition rate, reported in tons per square mile per year ($tons/mi^2/yr$), milligrams per square meter per month ($mg/m^2/mo$), etc.

The culminating concern is with transfer rates, involving the human body, through inhalation and ingestion followed by retention and absorption into fluids and tissues, and, finally, excretion, all of which are commonly expressed in micrograms per day, micrograms per kilogram of body weight per day, or, even, as micrograms per square meter of body surface.

D.3 UNITS

1 m = 10^6 μm = 10^2 cm = 10^{-3} km = 3.281 ft = 39.37 in

1 m^2 = 10^4 cm^2 = 10^{-6} km^2 = 10.76 ft^2 = 1550 in^2

1 m^3 = 10^6 cm^3 = 999.97 liters = 35.31 ft^3 = 6.1 x 10^4 in^3 = 264.2 gal

1 g = 10^6 μg = 10^3 mg = 10^{-3} kg = 0.035 oz = 0.0022 lb

1 tonne (metric) = 1000 kg = 10^6 g = 1.1023 tons (short)

D.4 CONCENTRATION CONVERSION FACTORS

1 ppb (mass) = 1 ng/g = 1μg/kg
1 ppm (mass) = 1 μg/g = 1 mg/kg
1 mg/liter (water) ≃ 1 ppm ≃ 1μg/g
1 μg/liter (water) ≃ 1 ppb
1 μg/d1 (blood) ≃ 0.95 μg/100 g (blood)

D.5 TRANSFER RATE CONVERSION FACTORS

1 mg/m^2/mo = 2.85 x 10^{-3} tons (short)/mi^{-2}/mo
1 tonne/yr = 2.74 kg/day = 1.1023 tons (short)/yr
1 μg/day = 3.53 x 10^{-8} oz (av.)/day

APPENDIX E

ABSTRACT OF A REVIEW OF THREE STUDIES ON THE EFFECTS OF LEAD SMELTER EMISSIONS IN EL PASO, TEXAS

Presented by Warren R. Muir
Council on Environmental Quality
Washington, D.C.
At the International Conference on Heavy
Metals in the Environment
Toronto, Ontario, Canada
October 1975

The committee reviewed two independent studies conducted in 1973 by Dr. Landrigan (CDC) and Dr. McNeil (ILZRO) to determine the effects of community lead exposures near the ASARCO smelter in El Paso, Texas. The CDC study used a random sample approach to group participating children, and in the ILZRO study match paired groups were selected on the basis of residence. In both studies the criteria for subclassification with regard to lead exposure were blood lead levels. Neuropsychological dysfunction was evaluated by several tests including WISC, WPPSI, and McCarthy scales. Statistical differences in test results could not be directly correlated to blood lead levels.

The opinion of the committee was that no firm conclusions could be drawn from the studies as to whether or not there are subclinical effects of lead on children in El Paso and that the reports and data made available have not clearly demonstrated any psychologic or neurologic effects in the children under study. It noted the absence of major chronic clinical effects, and concluded that these studies therefore do not bear upon the conclusions of other investigations under different conditions and those in which clinical effects have been confirmed. However, because of inherent problems of study design and the limitations in the tests used, this finding should not lead to a conclusion that low levels of lead have no effects on neuropsychological performance. Ellen Silbergeld, Ph.D., NIH, Eileen Higham, Ph.D., and Mr. Russell Jobaris, Johns Hopkins University, Department of Medical Psychology, served as special consultants.

The committee decided to limit its focus to a review of the three studies, and to attempt to account for and interpret the differences between the studies. Thus, aspects not related to differences were not emphasized.

The committee limited its consideration to the following materials: (1) reports of the three studies under consideration; (2) other materials provided by the authors of the studies; (3) background information and documents collected by Dr. Muir in El Paso. This presentation today consists of excerpts from a draft committee report.

E.1 HISTORY

El Paso is situated on the Mexican border in the western part of Texas. A lead smelter owned by American Smelting and Refining Company (ASARCO) has been located on the southwestern border of the city, on the Rio Grande River, since 1887. The area most conspicuously involved in the studies, Smeltertown, was a 2 x 6 block area located between the plant and the river. Smeltertown is no longer in existence, having been destroyed in December 1972. About 2 km south of Smeltertown is Old Fort Bliss, a considerably smaller community, whose inhabitants were considered in some, but not all, of the studies.

The ASARCO smelter produces lead, zinc, copper, and cadmium. Particulate matter is removed from airborne wastes in a series of baghouses; remaining emissions contain approximately 40 lb of lead per day.

The El Paso City County Health Department began an investigation of the ASARCO smelter in early 1970, in preparation for an air pollution suit filed by the city in April 1970. As part of this investigation, Dr.

Bertram Carnow was hired by the city as a consultant. At his suggestion, the city began to sample the blood lead levels of El Paso children to determine whether any had been over-exposed to lead. This included a large number of Smeltertown children. Based upon early results in 1971, Dr. Carnow visited El Paso, and saw a selected group of children with high blood lead levels. He interviewed the children, and reviewed their medical records. The information contained in the medical histories, and Dr. Carnow's interviews, constitute the observations reported by Dr. Carnow in the paper presented to the American Pollution Control Association (APCA). The clinical observations were in a paragraph of a paper otherwise devoted to a consideration of the effects of the smelter on the environment as a whole, and the extent of its emissions. This report contains no details on the age, exposures, individual signs and symptoms, or diagnostic criteria used in the ten cases reported. Our committee focused its attention, therefore, upon the two full-scale follow-up epidemiological studies conducted by Dr. Landrigan (CDC) and Dr. McNeil (ILZRO).

In 1973 ASARCO began a separate investigation of the population of Smeltertown, and asked Dr. James McNeil of the International Lead Zinc Research Organization (ILZRO) for his assistance in the examination and possible treatment of children with elevated blood levels greater than 60 mg/100 ml.

As a result of public concern over widespread lead poisoning throughout the city of El Paso, the mayor requested aid from the Federal Government. A separate protocol for a Center for Disease Control (CDC) study was submitted to and approved by the Public Health Board in 1973 with the understanding that the two studies would proceed independently, with those children in the ILZRO sponsored study being excluded from the CDC study.

In the summer of 1973, CDC and ILZRO proceeded independently to collect data for their respective studies. CDC's examinations were done in two weeks in June 1973, while McNeil's were carried out over the course of the summer with the aid of the El Paso public school system.

The CDC group supplied to the Committee data in detail, which were sufficient to allow the committee to conduct statistical tests and analyze characteristics of groups. For the ILZRO study, this committee requested data sufficient to carry out similar in-depth analyses. All of the requested data were supplied; however, they were not in such a form as to allow recalculation of most of the statistical findings of the study or to allow comparison with the CDC findings.

E.2 STUDY DESIGN

The environmental sampling that was performed was common for both of these studies. In the selection of study and control populations, the Landrigan CDC study used a classical approach of a random sample survey to determine the prevalence of abnormal blood lead values. The 13 census tracts most adjacent to the smelter were divided into three areas. The sampling frame was designed to obtain about 100 study subjects from each area for various age groups. Of 833 occupied residences, interviews were obtained from 758 study subjects in the 1-19 age group. The participating children were divided into a lead-absorption group (40-80 μg/100 ml) of 46 and a control group (< 40 μg/100 ml) of 78. There is no detailed description as to how the children were chosen.

CDC used these same children as the basis for the later study of neuropsychological dysfunction. All but 3 children chosen for study came from the 1972 prevalence survey; 5 children with known preexisting defects such as with a history of symptoms compatible with acute lead poisoning or acute lead encephalopathy and those who had received chelation therapy were excluded.

While it is understood that a number of Smeltertown children with blood lead levels over 40 μg/100 ml were eventually involved in litigation, most of them took part in the studies. However, on the recommendation of the lawyers representing the children, at least one group of 18 did not participate in the ILZRO study. In the absence of identification by names of the individuals in the three studies, it has been impossible to evaluate the effects of non-participation.

The ILZRO study was very different; 138 children from Smeltertown agreed to participate in a study. Residence, not blood lead, was the selection criterion. Two control groups were chosen, and were reported to have been matched on age, sex, ethnic background, and income, with one set chosen from El Paso and another set for those 8 years of age or under from a rural area about 12 miles from the smelter. This classification had the effect of grouping together children who, under the CDC criteria, would have been in "lead" and "control" groups.

The criteria used for subclassification of children with regard to lead exposure were based in both studies on the blood lead level. Whereas the CDC study utilized blood lead values obtained at only two points in time, ILZRO, which was faced with the problem that many children had repeated blood lead measurements with marked variations over a period of 18 months (the levels being generally lower after exposure was discontinued), classified children on the basis of the average of the "two highest" recorded values.

This criterion results in a substantial increase in the number of children in the apparently higher blood lead category and a corresponding decrease in the number of those in the apparently lower blood lead level category.

Although it is understandable that this type of selection was used to avoid underestimating the problem of lead intoxication in the population examined, it ultimately resulted in muddling of the separation between groups (and possibly obscuring eventual differences). For example, the selection for analysis of children from the same geographical area, subclassified according to blood lead level, in the ILZRO study, may give the impression that the effects of lead itself are being studied in a homogeneous population. However, since exposure was geographically the same, other factors inherent to each individual child may be responsible for the difference in blood lead level observed.

An additional method of classification could have been the use of free erythrocytic protoporphyrin measurements (FEP) which have been shown to provide an indication of metabolic effects of lead absorption on metabolism, particularly useful in blood lead level ranges (40-60 μg/100 ml) where analytical and biological fluctuation may result in uncertain classification. (The ILZRO study included this test but did not include it as a basis for data analysis.) Absence of elevation of free erythrocytic protoporphyrin may indicate those instances where high blood lead levels were spurious.

The following psychometric tests were employed by the two studies:

1. Wechsler Intelligence Scale for Children, WISC (CDC, ILZRO)
2. McCarthy Scales of Children's Abilities (ILZRO)
3. Wechsler Preschool and Primary Scale of Intelligence, WPPSI (CDC)
4. Lincoln-Oseretsky Motor Development Scale (ILZRO)
5. California Test of Personality Adjustment (ILZRO)
6. Frosting Perceptual Quotient (ILZRO)
7. Bender Visual-Motor Gestalt Test (CDC, ILZRO)
8. Peabody
9. WRAT
10. Wepman
11. Draw-a-person

All of the tests selected by both studies were appropriate for the ages of the children to whom they were administered. Since the common ground for these studies is the WISC test, with the WPPSI used by CDC and the McCarthy Scales by ILZRO for the younger children in their studies, the Committee concentrated on these three tests and the results obtained for them.

E.3 RESULTS

The study by CDC reports results for 27 children given the WPPSI (12 with blood lead levels 40-80 μg/100 ml and 15 with blood lead levels less than 40 μg/100 ml) and for 97 children tested with the WISC (34 in the "lead group" and 63 in the "control group"). Statistical analyses were performed on grouped data with one-tailed tests. Significant differences between lead and control groups are reported in this study for the performance IQ's of the WICS and WPPSI. In subtest scores, significant differences were found in Coding on the WISC and Geometric Design on the WPPSI. When data from both tests are combined, a significant difference between lead and control groups on performance IQ is found. No differences were found between groups in verbal IQ's or full-scale IW's of the WISC or WPPSI.

The ILZRO study based on match pairing solely by residences reports no significant differences in scores on the WISC or McCarthy scales between groups with increased lead absorption and pair-matched controls. Statistical analysis was by means of two-way analysis of variance by age and blood lead levels.

The two studies base much of their conclusions upon psychometric and neurological testing of children from El Paso and Smeltertown. The reported significant differences and psychometric and neuromotor functions in the CDC study were clouded by potentially important methodological difficulties. These included age differences between case and control groups, limited statistical treatment of the psychometric data collected, and, in the ILZRO study, the use of an average of the two highest blood lead levels to categorize lead exposure.

In addition, both the studies shared the following inherent problems:

1. Non-random exclusion of large groups of children
2. Uncertainties as to the selection of control groups
3. Reliance upon blood lead as the indicator of lead exposure and intoxication in analyses of data
4. Measurement of a limited aspect of psychological behavior
5. Lack of consideration of the potentially disruptive influences on test taking of the razing of Smeltertown, closing of its school, resettlement, litigation, and public controversy
6. Inability to rule out possible preexisting conditions

The Committee stressed the last issue, noting the likelihood that any behavioral or genetic factors that predispose an individual child to ingest or absorb more lead than another child equally exposed may itself be correlated to he result of psychometric testing. In other words an increased blood lead level may reflect, rather than cause, a preexisting difference in intelligence or behavior, an issue inherent in virtually all retrospective studies of the effects of low level blood lead.

The opinion of the committee was that no firm conclusions could be drawn from the studies as to whether or not there are subclinical effects of lead on children in El Paso and that the reports and data made available have not clearly demonstrated any psychologic or neurologic effects in the children under study. It noted the absence of major chronic clinical effects, and concluded that these studies therefore do not bear upon the conclusions of other investigations under different conditions and those in which clinical effects have been confirmed. However, because of inherent problems of study design and the limitations in the tests used, this finding should not lead to a conclusion that low levels of lead have no effects on neuropsychological performance.

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